NEW ZEALAND HEALTH TECHNOLOGY ASSESSMENT (NZHTA)
THE CLEARING HOUSE FOR HEALTH OUTCOMES AND
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Effectiveness of therapeutic agents in the treatment of asthma

A critical appraisal of the literature

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DISCLAIMER

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LIST OF ABBREVIATIONS

Δ	=	change in
%PV	=	% of predicted value
AUC	=	area under curve
av	=	average
bd	=	twice daily
BDP	=	Budesonide
BEC	=	Beclomethasone
BMB	=	Bambuterol
cf	=	compared with
CFC	=	chlorofluorocarbon propellant
CIR	=	Circulaire™
CNV	=	Conventional nebuliser
CO	=	randomised controlled trial, cross over design
CON	=	Continuous dose
COPD	=	Chronic obstructive pulmonary disease
CYC	=	Cyclohaler
D/A	=	Diskus/Accuhaler
D-inh	=	diskhaler
DPI	=	Dry powder inhaler
DU	=	Diskus
ED	=	Emergency department
FEV_1	=	Forced expiratory volume in one second
FNS	=	Flunisolide
FP	=	Fluticasone
FRM	=	Formoterol
HFA	=	hydrofluoroalkane propellant
ICS	=	Inhaled corticosteroids
ICU	=	Intensive care unit

IM	=	intramuscular
inh	=	inhaler
int	=	Intermittent dose
IPR	=	Ipratropium
ITT	=	intention to treat
IV	=	intravenous
MA	=	meta-analysis
mane	=	once in morning
MDI	=	metered dose inhaler
mg	=	milligrams
MNT	=	Montelukast
N/A	=	Not applicable or not available
neb	=	nebuliser
NNH	=	numbers needed to harm using the drug of least efficacy to achieve one unfavourable outcome over a period of time (study duration in this report)
NNT	=	numbers needed to treat using the drug of efficacy to achieve one favourable outcome over a period of time (study duration in this report)
nocte	=	once at night
n.s.	=	not statistically significant
OCS	=	Oral corticosteroids
PC_{20}	=	challenge (usually methacholine or histamine) concentration that caused a 20% fall in FEV_1
PEFR	=	Peak expiratory flow rate
po	=	oral
PRD	=	Prednisone
PRN	=	as required
q4h	=	every four hours
qd	=	once daily
Qid	=	four times daily
QoL	=	Quality of life
RCT	=	randomised controlled trial

ROT	=	Rotahaler
se	=	standard error
SLB	=	Salbutamol
SLM	=	Salmeterol
SOB	=	shortness of breath
SR	=	systematic review
TAA	=	Triamcinolone
TBH	=	Turbuhaler
TEB	=	Terbutaline
THP	=	Theophylline
μg	=	micrograms
URTI	=	upper respiratory tract infection
ZAF	=	Zafirlukast

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Scope of systematic review of asthma pharmaceuticals

The development of this systematic review protocol involved extensive consultation between the NZHTA and the Pharmaceuticals sub-committee of the Asthma Working Group of the New Zealand Asthma Guideline Group.

SEARCH METHODOLOGY

Search strategy

Searches were restricted to information published from 1st January 1997 onwards, in all languages. Original searches were carried out in December 2000. An update of Pre-Medline, Current Contents and the Science Citation Index was performed in March 2001.

An additional very broad combined search of the Pre-Medline, Medline, Embase, Current Contents, and Cinahl databases for papers on any aspect of asthma in New Zealand was also completed in March 2001.

Principal sources of information

The following databases were searched using the search strategies outlined in Appendix 1:

Bibliographic databases

- Medline
- Embase
- Current Contents
- Science Citation Index
- Cinahl
- Cochrane Library Controlled Trials Register
- Index New Zealand

Review databases

- Cochrane Library Systematic Reviews & Protocols
- Database of Abstracts of Reviews of Effectiveness
- NHS Economic Evaluation Database
- Best Evidence

Library catalogues

- New Zealand Ministry of Health library
- New Zealand Bibliographic database - Te Puna
- US National Library of Medicine
- World Health Organisation

Websites

- Health Canada
- US Centers for Disease Control
- British Thoracic Society
- EGuidelines (UK)
- University of Dundee Asthma Research Unit
- UK General Practice Airways Group
- UK Department of Health publications
- Meta-register of Controlled Trials

- TRIP - Turning Research into Practice
- Health Evidence Bulletins Wales
- OMNI - Organised Medical Networked Information
- European Federation of Asthma and Allergy Associations
- GINA - Global Information Network on Asthma
- Canadian Office for Health Technology Assessment
- Canadian Network for Asthma Care
- Canadian Lung Association
- Canadian Thoracic Society
- Asthma Society of Canada
- ClinicalTrials.gov
- American Academy of Allergy Asthma and Immunology
- JAMA Asthma Information Center - Physicians Section
- US National Heart, Lung, and Blood Institute
- US Asthma Clinical Research Network
- US National Institute of Allergy and Infections Diseases
- Thoracic Society of New Zealand and Australia
- Australian Department of Health & Aged Care
- Ministerial Asthma Working Party

Note: hand searching of journals, contacting of manufacturers, or contacting of authors for unpublished research was not undertaken during the search process.

Major search terms used

- index terms from Medline (MeSH headings): asthma, asthma-drug therapy, anti-asthmatic agents, bronchodilator agents, randomized controlled trials, controlled clinical trials, meta-analysis, guidelines, practice guidelines, double-blind method, single-blind method, comparative study, treatment outcome
- index terms from Embase: asthma, asthma-drug therapy, randomized controlled trial, drug comparison, double-blind procedure, single-blind procedure, meta-analysis
- additional keywords used (not standard index terms): systematic review, systematic overview, effectiv*, efficacy
- keywords used for exclusions: child* , infan*, pediatric*, paediatric* *as title words* when adult* was *not also* in the title; copd, chronic obstructive, rhinitis, *as title words* when asthma was *not also* in the title

Search filters used to identify randomized controlled trials, meta-analyses, and guidelines in the literature were adapted from those produced by the Center for Reviews and Dissemination at the University of York.

The complete search strategies are given in Appendix 1.

STUDY INCLUSION CRITERIA

Studies published in English, French and German language from 1997 onwards (final search completed March 2001) are included. The population of interest is defined as adults with acute or chronic asthma, including aspirin and exercise induced asthma. A strict definition of adult based on age inclusion criteria has been avoided. Where both children and adults make up the study population these studies have been included.

Studies conducted in hospital, emergency department, outpatient clinic, general practitioner and pharmaceutical usage settings are included. Only randomized controlled trials and systematic reviews and meta-analyses (as a subset of systematic reviews) of randomized controlled trials are included. Systematic reviews were only included if the researchers searched Medline and at least one other database.

Studies conducted using double blinding are included. If no double blinding studies in a particular class comparison were available then studies conducted using single blinding were included or open if no double blinding or single blinding studies were available in a particular class comparison.

Only studies with an enrollment sample size of 30 patients or more have been included**.**

Only drugs available in New Zealand were included in the review.

STUDY EXCLUSION CRITERIA

Studies were excluded if they included:

- any patients with Chronic obstructive pulmonary disease (COPD)
- only children (classified as 12 years or younger or an article using the term 'child' or 'children' or 'paediatric' or 'pediatric')
- any patients who were pregnant
- a pharmacoeconomic analysis alone
- a comparison between efficacy drug and placebo alone. Exclusions: Immunotherapy
- letters, non-systematic reviews, editorials and comments were also excluded.

THERAPEUTIC INTERVENTIONS

Following is a list of the main systematic review comparisons between different classes of asthma medications:

Anticholinergics combined with short-acting β-agonists v short-acting β-agonists
Long-acting β-agonists v long-acting β-agonists
Long-acting β-agonists v short-acting β-agonists
Long-acting β-agonists v inhaled steroids
Long-acting β-agonists v leukotriene antagonist
Long-acting β-agonists v oral β-agonists
Long-acting β-agonists v theophylline
Short-acting β-agonists v short-acting β-agonists
Short-acting β-agonists v inhaled steroids
Short-acting β-agonists v theophylline
Short-acting β-agonists v nedocromil
Inhaled steroids v inhaled steroids
Inhaled steroids v oral steroids
Inhaled steroids v leukotriene antagonists
Inhaled steroids v theophylline
Leukotriene antagonists v cromoglycate
Leukotriene antagonists v theophylline
Acupuncture v other treatment
Immunotherapy v placebo
Device v device
CFC propellant v HFA propellant

Several relevant interventions have been subjected to Cochrane Reviews. Topics covered include immunotherapy, acupuncture, antileukotrienes compared to inhaled corticosteroids, corticosteroids in acute and post-acute asthma, holding chambers versus nebulisers in acute asthma, long-acting beta-agonists versus theophylline and nedocromil for preventing exercise induced bronchoconstriction. The studies covered in these reviews have been excluded from individual appraisal. The Cochrane systematic reviews themselves have been included as high quality appraised literature. Only studies meeting the following criteria have been appraised in intervention areas covered by these Cochrane reviews:

- sample size greater than 100
- published after the latest substantial amendment to those Cochrane reviews.

PATIENT OUTCOMES

Studies with all or some of the following patient outcome endpoints have been included. These relate to commonly assessed POEM (Patient Oriented Evidence that Matters) endpoints.

Endpoints:

- relapse
- rescue medicine use
- symptom ratings
- quality of life
- spirometric outcomes (e.g. FEV_1, PEFR)
- methacholine challenge
- exercise challenge
- time to onset of effect and maximal effect
- safety endpoints – cortisol, bone density, pulse, BP, tremor
- health care usage – hospital admission, ED attendance, length of stay

STUDY SELECTION

Studies were selected for appraisal using a two-stage process. Initially the titles and abstracts (where available) identified from the search strategy were scanned and excluded as appropriate. The full text articles were retrieved for the remaining studies and these were appraised if they fulfilled the study selection criteria outlined above.

There were 1292 studies identified by the search strategy (see appendix 1). Two hundred and ninety two full text articles were obtained after excluding studies based on examination of the search titles and abstracts. A further 164 of these full text articles did not fulfil the inclusion criteria. Therefore 128 articles were fully appraised and are included in this report.

EVIDENCE TABLES

Key information summaries include study reference, study design, study grading, treatment arms, patient inclusion and exclusion criteria, number of patients randomized, primary and secondary efficacy results with p-values and/or 90%/95% confidence intervals and comments on internal validity issues arising from the study appraisal. Number needed to treat (NNT) was calculated when sufficient information was presented to allow calculation of this statistic.

Unless otherwise stated the drug(s) of efficacy are presented in the left-hand column of the results section. P-values unless otherwise stated relate to between treatment group comparisons. Refer to Appendix 2 for detailed description of table items.

All studies were appraised using modified SIGN (Scottish Intercollegiate Guidelines Network) methodology checklists (see Appendix 3). The evaluation criteria are defined by a series of questions covering study internal validity. These questions addressed the quality of the study research question(s), randomisation methods, study population demographics, concealment and blinding methods, type of outcome measures, study group treatment regimens, patient dropout rates and statistical power adequacy, intention to treat (ITT) analysis methodology and the degree of industry support.

For systematic reviews and meta-analyses appraisal questions addressed the review methodology, literature search rigour, potential benefits and harms of intervention and the synthesis and conclusions drawn by combining studies in the review.

The final grading (1++, 1+ or 1-) code was allocated based upon the study design and study quality.

For a study to receive a 1++ grading the following criteria needed to be fulfilled:

- clearly defined study question
- a clear description of an adequate randomisation process
- absence of baseline differences in demographic variables, markers of asthma severity and other potential confounding variables between intervention groups post-randomisation
- an adequate concealment method and use of double blinding
- outcomes measured in a standard, valid and reliable way

- all study arms treated equally
- at least 80% of the sample randomised were included in the presented analyses
- an ITT analysis was presented
- pharmaceutical company involvement was restricted to either funding alone or no involvement.

Factors that automatically consigned studies to a 1- grading included:

- open study
- study groups were not treated equally
- ITT analysis not presented
- significant omissions or errors in patient demographic information and outcome results.

Combinations of two or more of the following also resulted in a 1- grading:

- baseline study differences, single blind, less than 80% of the participant's randomised were analysed, and pharmaceutical company staff were included at authorship level.

All other studies were graded as 1+.

Study limitations

Systematic reviews are limited by the quality of the studies included in the review and the methodology of the systematic review.

In the review of asthma therapeutic agents the quality of the included articles was such that there were no studies graded as 1++. Ninety-one of 128 (71%) were graded as 1+ and 37 of 128 (29%) as 1-. Ordinarily 1- studies would be excluded from a systematic review. They were included on this occasion so the therapeutics arm of the asthma guidelines group could assess them for relevance to the development of the New Zealand based guideline. However, the results of these studies should be viewed with considerable caution.

Common limitations to the study designs included:

- lack of description on the study methodology
- differences between study groups post randomisation or a lack of comparison between key variables post randomisation (particularly in studies using the cross over design)
- use of open and single blind designs
- inadequate power
- not using an ITT analysis
- pharmaceutical company involvement in all aspects of the study.

Individual study limitations are described in the comments section of the evidence tables.

Limitations to the review methodology that need to be considered in developing an asthma therapeutics guideline include restriction to:

- articles published from 1997 onwards
- the published literature
- English, French and German language articles
- reviewing each study by one researcher only
- study evaluation criterion did not cover aspects of statistical methodology such as the appropriateness of the data collected and the statistical tests used to analyse this.

In developing a guideline for asthma therapeutics consideration will need to be given to studies published pre 1997. The vast majority of articles of interest were published in the pre 1997 time period so methods should be developed by the guidelines group to assess whether the new evidence presented in this review is sufficient to alter any recommendations included in previous evidence based guidelines.

Restriction to the published literature is likely to lead to bias since the unpublished literature tends to consist of studies not identifying a significant result.

Restriction by language may result in study bias but the direction of this bias cannot be determined.

Although two researchers appraised the articles included in this review they did not cross validate the data extraction and appraisal process.

The majority of articles appraised were not set in New Zealand. Therefore, the generalisability of these studies to the New Zealand setting needs to be considered.

The studies were initially selected by examining the abstracts of these articles. Therefore, it is possible that some studies were inappropriately excluded prior to examination of the full text article.

There is a limitation on space in evidence tables. Therefore, study details have been summarised rigorously. In particular, inclusion and exclusion criteria listed in the tables represent a small proportion of the criteria most articles provided. In general, data about the basis of the diagnosis of asthma has not been included and common exclusion criteria such as pregnancy have not been included in the tables.

The comment “pharmaceutical limitations” indicates the presence of restrictions on pharmaceutical agents used by study participants but the reader is referred to the individual studies for more detail as required. The phrase “pharmaceutical company funded and supported trial” is commonly encountered in the comments section. This indicates pharmaceutical companies have provided both financial support and investigational support in the form of staff inclusion among the study authors.

This review was conducted over a limited time frame (November 2000 – April 2001).

Evidence Tables

Anticholinergic:

Acute asthma

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma

Study Source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Rodrigo and Rodrigo 2000) RCT Grade 1+ Country: Uruguay	Salbutamol mdi 120 µg/puff + Ipratropium mdi 21 µg/puff in a dose of 4 puffs at 10 min intervals (480 µg/84 µg) V Salbutamol mdi 120 µg/puff in a dose of 4 puffs at 10 min intervals (480 µg) 3 hours of treatment (24 puffs or 2,880 µg salbutamol and 504 µg ipratropium per hour)	Inclusion: Age 18-50 yrs FEV_1/PEFR < 50% PV	180		SLB+IPR	SLB	*P* value	NNT	• Mean age 35 and female 37%, PEFR 32%PV in SLB+IPR group; mean age 33 and female 34%, PEFR 33%PV in SLB group • Acute asthma, Emergency Department setting
				Improvement over salbutamol control group %					
				PEFR (95%CI)	+20% (2.6,38.4)		*P*=.02		
				FEV_1 (95%CI)	+48% (19.8,76.4)		*P*=.001		
				Hospital admissions n (%)	18 (20%)	36 (39%)	*P*=.01	5	
				Pre ED use of β-agonists by ipr patients: increase in FEV_1					
				previous use	N/A	N/A	*P*=.01		
				no previous use	N/A	N/A	*P*=.03		
				Symptoms					
				24+ hours	N/A	N/A	*P*=.01		
				< 24 hours	N/A	N/A	*P*=.09		
				$FEV_1 \leq$ 30PV%	N/A	N/A	*P*=.001		
				> 30PV%	N/A	N/A	*P*=.60		

Study design abbreviations
RCT = Randomised controlled trial, parallel design
CO = randomised controlled trial, cross over design
MA = meta-analysis
SR = Systematic review

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Weber et al. 1999) RCT Grade 1+ Country: United States	All patients received prednisone po 60 mg Salbutamol neb 10 µg/hour + Ipratropium neb 1.0 µg/hour V Salbutamol neb 10 µg/hour + Ipratropium neb 1.0 µg/hour ≤ 3 hours of treatment	Inclusion: Age 18+ yrs FEV_1/PEFR < 70% PV after 2.5 mg Salbutamol in 3 mL normal saline	67		SLB+IPR	SLB	*P* value	• Mean age 46 and female 75%, PEFR 50%PV and smoking history 48% in SLB+IPR group; mean age 49 and female 66%, PEFR 40%PV and smoking history 74% in SLB group • Significant *P*<.05 baseline differences in PEFR%PV and smoking history. *P*<.10 differences in previous hospitalization and intubation • Results have been adjusted for baseline differences • Acute asthma, Emergency Department setting • Pharmaceutical (producer of ipratropium) involvement in supply of ipratropium and pharmacy costs
				Improvement over salbutamol control group % PEFR (95%CI)				
				Adjusted for baseline PEFR	+6.3% (-1.5,27%)		*n.s.*	
				Median length of stay (minutes)	210	245	*P*=.03	
				Adjusted for baseline PEF	N/A	N/A	*P*=.26	
				Hospital admissions n (%)	8 (23%)	13 (39%)	N/A	
				Adjusting for baseline PEF OR (95%CI)	0.88 (0.28, 2.8)			

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Lin et al. 1998) RCT Grade 1+ Country: United States	Salbutamol 2.5 mg + Ipratropium 0.5 mg (first dose only) then every 20 min 2 more doses of salbutamol only (total 3 doses) neb V Salbutamol 2.5 mg + placebo (first dose only) then every 20 min 2 more doses of salbutamol only (total 3 doses) neb Treatment period 1 hour	Inclusion: Age 18+ yrs PEFR <200 L/min Exclusion: 20 pack years+ smoker β-agonists preceding 4 hours	55		SLB+IPR	SLB	*P* value	NNT	• Mean age 40 and female 54% in SLB + IPR group, mean age 41and female 59% in SLB group • Acute asthma. Convenience sample selected from Emergency Department
				Number of patients admitted to hospital n (%)	3 (11%)	10 (36%)			
				Difference and 95%CI of proportion admitted	25% (3%,46%)		*P*=.03	4[1]	
				PEFR L/min mean			Over 1 hour		
				BL	131	142	period		
				20 min	197	197			
				40 min	252	218			
				60 min	269	228	*P*=.001		
				PEFR L/min %PV mean					
				BL	28	29	Over 1		
				20 min	42	37	hour		
				40 min	53	45	period		
				60 min	57	47			
							P<.001		

[1] NNT calculated using the formula NNT= 1/Absolute risk reduction. Therefore, the number needed to treat to avoid one admission was 1/0.25 (ie. 4) for combination therapy of one hour duration compared with salbutamol alone for one hour.

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Rodrigo et al. 1999) MA Grade 1+	Ipratropium inh 0.5 µg (single dose) plus β-agonists (Salbutamol 8 studies, fenoterol 2 studies) after arrival in ED V β-agonists alone First 90 minutes of treatment	Inclusion: Age 16+ yrs English language studies RCT, double blind Patients with acute asthma, treated in ED with β-agonists Search: 1978-1999 (April) MEDLINE, Science Citation Index, Current Contents, reviews (articles and primary research), experts	1483		β-agonist + IPR	*P* value	NNT	• 10 studies included, acute asthma, mean age 32 ± 13 years and female 64% • Mean methodology quality score 0.66 (max = 1) • Criteria for discharge and admission not clearly defined • Reported adverse effects not assessed nor delivery devices
				Overall effect size (std units) cf. control group				
				FEV_1 (95%CI)	0.14 (0.04,0.24) (10%) (2%, 18%)	*P*=.008		
				Homogeneity test		*P*>.5		
				Study specific effects	(0.03-0.63)	N/A		
				Mean FEV_1 at admission <35%PV (4 studies) (95%CI)	0.38 (0.09,0.67)	N/A		
				Use of corticosteroids (7 studies) (95%CI)	0.14 (0.00,0.28)	N/A		
				Hospital admissions (5 studies) (Odds Ratio, 95%CI)	0.62 (0.44,0.88)	*P*=.007	18	

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes		Comments
(Stoodley et al. 1999) MA Grade 1+ Country: Canada	Ipratropium plus β-agonists mdi or neb after arrival in ED V β-agonists alone 30-90 minutes duration of treatment	Inclusion: Age 18+ yrs RCT (double blinding not necessary but all included studies double blind) Patients with acute asthma, treated in ED or similar with β-agonists Search: MEDLINE (1966-97), EMBASE (1980-97), CINAHL (1982-97), Biological Abstracts (1990-97), Cochrane database and Current Contents (1996-97)	1377		β-agonist + IPR	• 10 studies included, acute asthma, mean age range for treatment group 29.5-50.4 years, control group 29.6-53.2. • Study quality assessment limited to randomization, double blinding and inclusion of data for dropouts and withdrawals • Dosages of ipratropium not specified • Changes in airflow assessment FEV_1 (4 studies) PEFR (5 studies) both (1 study) • Significant Cochran Q test for homogeneity (p=.047) suggesting included trials were a heterogeneous group. One trial had much lower baseline PEFR values. Removal resulted in Q test P= .37, summary effect value 0.35 (.24,.47). Study results reported including 10 studies.
				Overall effect size (std units) cf. control group PEFR/ FEV_1 (95%CI)	0.38 (0.27,0.48)	
				% improvement in FEV_1 (4 studies)	7.3% (3.8%, 10.9%)	
				% improvement PEFR (5 studies)	22.1% (11.0%, 33.2%)	
				Hospital admissions (3 studies, n=1064) (Relative Risk, 95%CI)	.73 (53, .99)	
				Effect size of studies with IV steroids (4 studies) to all enrolled patients	.25 (.10,.40)	

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study Source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Garrett et al. 1997) RCT Grade 1- Country: New Zealand	All patients received IV hydrocortisone 200 mg within 15 minutes of treatment start (Combivent)™ Ipratropium neb 1.5 mg in a dose + Salbutamol neb 2.5 mg V Salbutamol neb 2.5 mg Duration 90 minutes	Inclusion: Age 18-55 yrs FEV_1< 70% PV Exclusion: Smoking history of 10+ pack years Complicating illness eg COPD	338		SLB + IPR	SLB	*P* value	NNT	• Mean age 30 and % female not specified, FEV_1 40%PV in SLB+IPR group; mean age 30, % female not specified, FEV_1 40%PV in SLB group • Overall % female 61%, 17% Maori, 24% Pacific Island ethnicity • 13% of patients reported using OCS, 32% ICS, 80% inh β-agonist within 6 hours of presentation to ED • Acute asthma, Emergency Department setting • No intention to treat based analysis, 58 patients (27 in combivent™ group and 31 in salbutamol group) withdrawn after treatment received (no FEV_1 recorded). • Pharmaceutical company supported study
				Mean absolute difference over salbutamol group					
					40 (57)				
				Baseline FEV_1ml (se)[1]	93 (24)		*P*=.4485		
				45 minutes	113 (18)		*P*=.03		
				90 minutes (primary efficacy)			*P*=.02		
				FEV_1< 1 L at baseline:					
				Δ FEV_1 (mls)	22		*n.s.*		
				FEV_1≥ 1 L/min at baseline:					
				Δ FEV_1 (mls)	176		*P*<.005		
				Hospital admissions (%)	15.3%	22.3%		14	

[1]se = standard error

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(FitzGerald et al. 1997) RCT Grade 1- Country: Canada	All patients received oxygen and IV bolus of 125 mg methyl-prednisone (within 15 minutes of nebulization) (Combination) Ipratropium neb 0.5 mg in a dose + salbutamol neb 3.0 mg V Salbutamol neb 3.0 mg Duration 90 minutes	Inclusion: Age 18-55 yrs FEV_1< 70% PV Exclusion: Smoking history of 10+ pack years COPD or significant other medical illness	342		SLB+IPR	SLB	*P* value	NNT	• Mean age 31 and female 60%, FEV_1 1.62L in SLB+IPR group; mean age 30, % female 64%, FEV_1 1.53L in SLB group • Prior asthma medication in combination and salbutamol alone groups: 12% and 12% of patients reported using OCS, 46% and 40% ICS, 88% and 90% inh β-agonist within 24 hours of presentation to ED • Acute asthma, Emergency Department setting • Poor description of randomisation, concealment and blinding methodology • Not strict intention to treat based analysis • Criteria for discharge and admission not clearly defined • Pharmaceutical company partly funded study
				Mean change from baseline					
				Baseline FEV_1 L (se)	1.62 (0.05)	1.53 (0.05)	*n.s.*		
				45 minutes	0.58 (0.04)	0.52 (0.04)	*n.s.*		
				90 minutes (primary efficacy)	0.61 (0.04)	0.52 (0.04)	*n.s.*		
				Hospital admissions (%)	5.9%	11.2%		19	

Table 1: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kamei et al. 1999) RCT Grade 1- Country: Japan	Fenoterol 1 puff (200 µg/puff) every 1 minute for 5 minutes, total 1000 µg + Oxitropium bromide 2 puffs (100 µg/puff) every 1 minute for 5 minutes, total 1000 µg mdi with InspirEase™ holding chamber V Fenoterol 1 puff (200 µg/puff) every 1 minute for 5 minutes, total 1000 µg Treatment duration 60 minutes	Inclusion: FEV_1 < 70% PV Exclusion: Pulmonary emphysema Complicating drugs	69	At 60 minutes Mean value cf. baseline PEFR L/min (se) From baseline PEFR % impr 1 min 15 min 30 min 60 min	FRM + OTB 261 (18) N/A N/A N/A N/A	FRM 210 (17) N/A N/A N/A N/A	*P* value *P*<0.05 *P*<0.02 *P*<0.01 *P*<0.02 *P*<0.001	• Mean age 55 and female 46%, best FEV_1 1.81L in FRM+OTB group; mean age 56and female 65%, best FEV_1 1.86L in FRM group • Acute asthma, Emergency Department setting • Open study, no detail on randomisation nor statistical power • Intention to treat based analysis not evident, 31/34 and 33/35 in respective randomised groups analyzed for efficacy • Some data results for primary efficacy outcome not reported

Cromoglycate

Chronic asthma

Table 2: Summary of studies investigating the effect of pharmaceuticals (cromoglycate versus inhaled steroid) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Hoshino et al. 1998) RCT Grade 1+ Country: Japan	Ketotifen po 1 mg bd V Disodium cromoglycate (DSCG) inh 2 mg Qid V Beclomethasone inh 100 μg Qid 12 weeks	Inclusion: Age 16-50 yrs 20+% increase in FEV_1 or PEFR Daily/as needed β-agonists with no I/OCS previous 6 months Exclusion: FEV_1 PV < 50% Smoker I/OCS or DSCG in previous 4 months	32	12 weeks Asthma symptoms Median FEV_1 (%PV) Before After Median PEFR(L/min) Before After	Ketotifen 72.0 80.0 *n.s.* 450 500 *n.s.*	DSCG 63.2 72.5 *P*<.05 350 450 *P*<.01	BDP 66.0 74.3 *P*<.05 425 475 *P*<.01	*P* value DSCG v Ketotifen *P*<.01 BDP v Ketotifen *P*<.05 DSCG v Ketotifen *P*<.05 BDP v Ketotifen *P*<.05	• N=13, mean age 27 and female 46%, FEV_1 72%PV, PEFR(l/min) 450 in ketotifen group; N=9, age 26 and female 33%, FEV_1 63%PV, PEFR(l/min) 350 in DSCG group; N=9, age 30 and female 30%, FEV_1 66%PV, PEFR(l/min) 425 in BEC group • Small numbers in study treatment arms. Baseline differences in FEV_1 PV% and PEF • The study also included analysis of fibreoptic bronchoscopy and immunohistochemistry data

Immunotherapy

Chronic asthma

Table 3: Summary of studies investigating the effect of pharmaceuticals (immunotherapy with placebo) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Bousquet et al. 1999) RCT Grade 1- Country: France	Sublingual immunotherapy with standardized *Dermato-phagoides pteronyssinus (DP)-D. farinae* (DF) 50/50 extract Progressive dosage from 1, 10, 100, 300 IR/ml daily for 4 weeks then 3 times a week for 24 months V Placebo 25 months	Inclusion: Age 7-42 years FEV_1 > 70%PV Clinical history of allergy to house dust-mites Exclusion: Patients on ICS >1000 µg daily, I/O β-agonists > 4 times daily Sensitization to animal danders Presence of a household pet	85		IMM	Placebo	*P* value	• Mean age 21 and female 45%, MCh PD_{20} mean 105 µg in IMM group; mean age 22 and female 42%, MCh PD_{20} mean 229 µg in placebo group • Significantly greater sensitivity to methacholine in active treatment at baseline • No strict intention to treat analysis. Detailed study outline shows 20 patients (24% or 10 in each group) discontinued within first 6 months of study not included in efficacy analysis at 11 & 25 months. Only 23/42 in IMM group and 27/43 patients in placebo completed 25 months. Safety efficacy evaluated at 25 months • QoL analysis includes only 38 (18/20) patients • Pharmaceutical company supported trial
				AM PEFR L/min (base)	404.1	415.7		
				Mean (last entry)	426.3	424.3	*n.s.*	
					P=.01	*n.s.*		
				PM PEFR L/min (base)	414.1	429.6		
				Mean (last entry)	433.2	437.7	*n.s.*	
					P=.03	*n.s.*		
				Nighttime asthma (base)	0.20	0.26		
				Mean (last entry)	0.17	0.11	*n.s.*	
					n.s.	*n.s.*		
				Daytime asthma (base)	0.32	0.37		
				Mean (last entry)	0.17	0.19	*n.s.*	
					P=.02	*n.s.*		
				QoL assessment scores				
				Mental health	79.7	60.7		
				Perception of health	76.5	56.8	*P*=.07	
				Physical pain	86.2	68.3	*P*=.01	
							P=.02	
				Safety assessment				
				Adverse events (no. pat/%)	15/42 (35.7%)	14/43 (32.6%)		
							P=.84	

Leukotriene antagonists

Chronic asthma

Table 4: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus leukotriene antagonists) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Villaran et al. 1999) RCT Grade 1+ Country: 12 countries	Salmeterol inh 50 µg bd V Montelukast po 10 mg daily 8 weeks	Inclusion: Age 15-45 yrs FEV_1 improved by ≥12% post β-agonist PC_{20} 0 in FEV_1 in response to ≤ 4mg/ml methacholine or histamine ≤ 20 pack years smoking Exclusion: Asthma requiring emergency care – past month	197		MNT	SLM	*P* value		• Mean age 27 and female 50% • Exercise induced bronchoconstriction • Pharmaceutical sponsored trial (producers of montelukast) • Similar study design, authors and sponsor to next study
				Maximal % fall in FEV_1 post exercise (cf. baseline)	17.2%	10.7%	*P* < .001		
				Recovery time to within 5% of prechallenge level at 8 weeks compared with pre intervention (min)	-23.9	-11.3	*P* = .002		
								NNH	
				Adverse respiratory events (SLM cf. MNT)	39%	54%	*P* < 0.05	7	
(Edelman et al. 2000) RCT Grade 1+ Country: United States	Salmeterol inh 50 µg bd V Montelukast po 10 mg nocte 8 weeks	Inclusion: Age 15-45 yrs FEV_1 ≥ 65%PV <15 pack-years smoking Exclusion: Asthma or URTI requiring emergency care – past month	191		MNT	SLM	*P* value		• Mean age 26 and female 50% • Mod-severe activity limitation in 60% in past month at baseline • No baseline ethnicity data presented • Pharmaceutical company input (producers of montelukast) in funding, design, conduct and analysis of trial
				Maximal % challenge fall in FEV_1	57.2%	33.0%	*P* = .002		

Table 4: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus leukotriene antagonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Busse et al. 1999a) RCT Grade 1+ Country: United States	Salmeterol inh 42 µg bd V Zafirlukast po 20 mg bd 4 weeks	Inclusion: Age ≥ 12 yrs FEV_1 50-80%PV Exclusion: >10 pack years tobacco smoking	289		SLM	ZAF	*P* value	NNT	• Mean age 38 and female 80% • Mean FEV_1 66%PV • 80% on inhaled steroid pre-study • Exercise induced bronchoconstriction • Unknown proportion of participants identified through advertisements – may limit generalisability
				Improvement in am PEFR (L/min)	29.6	13.0	$P \leq 0.001$		
				Symptom free days	22.4%	8.8%	$P \leq 0.001$	7	
				% days with no rescue medication use	30.5%	11.3%	$P \leq 0.001$	5	

Table 5: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus leukotriene antagonists) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Malmstrom et al. 1999) RCT Grade 1+ Country: Multinational	Beclomethasone inh 200 µg bd V Montelukast po 10 mg nocte V Placebo 12 weeks	Inclusion: Age ≥ 15 yrs FEV_1 50-85%PV Nonsmoker Exclusion: Pharmaceutical limitations	895		BEC	MNT	95%CI (diff)	NNT	• Median age 35 and female 61% • Mean FEV_1 65%PV • Pharmaceutical company funded and supported trial • Baseline differences in gender mix between interventions which were of uncertain significance • Unclear whether ITT analysis was used
				% Δ am FEV_1	13.1	7.4	3, 8.5		
				% Δ daytime symptom score	-0.62	-0.41	-0.33, -0.09		
				% Δ nocturnal awakenings (n/wk)	-2.4	-1.7	-1.08, -0.32		
							P value		
				Asthma attacks (% patients)	10.1	15.6	*P*<0.05	18	
(Bleecker et al. 2000) RCT Grade 1+ Country: United States	Fluticasone inh 88 µg bd V Zafirlukast po 20 mg bd 12 weeks	Inclusion: Age ≥12 yrs FEV_1 50-80%PV Exclusion: History of life threatening asthma Use of tobacco in past year or >10 pack-years total Resp infection within 2 weeks of screening Pharmaceutical limitations	451		FP	ZAF	*P* value	NNT	• Mean age 41 and female 50% • Mean FEV_1 68%PV • Supported by fluticasone producers
				Δ am FEV_1 (L)	0.42	0.2	*P*<0.001		
				Δ symptom free days (%)	28.5	15.6	*P*<0.001	8	
				Δ rescue free days (%)	40.4	24.2	*P*<0.001	6	
				Δ nights with no awakenings (%)	21.2	8.0	*P*<0.001	8	

Table 5: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus leukotriene antagonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Westbroek and Pasma 2000) CO Grade 1+ Country: Netherlands	Fluticasone inh 100 µg bd V Zafirlukast po 20 mg bd 2 weeks each	Inclusion: Age 18-70 yrs $FEV_1 \geq 50\%PV$ Non smoker Exclusion: Resp infection or asthma admission within a month of screening Pharmaceutical limitations	30		FP	ZAF	95%CI (diff)	• Mean age 45 and female 70% • Financial support from producers of fluticasone • No comparison of asthma severity at baseline • Adequate concealment could not be determined
				PC_{20} histamine (mg/ml)	1.61	0.99	0.05, 1.50	
				AM PEFR (L/min)	409	391	-0.08, 35.3	
(Laviolette et al. 1999) RCT Grade 1+ Country: 18 countries	Montelukast po 10 mg nocte + beclomethasone inh 200 µg bd V Beclomethasone inh 200 µg bd V Montelukast po 10 mg nocte V Placebo	Inclusion: Age ≥15 yrs FEV_1 50-85%PV Non-smoker Exclusion: Resp infection within 3 weeks of screening Pharmaceutical limitations	642		BEC/MNT	BEC	*P* value	• Mean age 39 and female 51% • Mean FEV_1 72%PV • Other study comparisons not presented in full • Baseline differences in placebo group from other interventions • Pharmaceutical company funded and supported trial
				% Δ am FEV_1	5.08	0.72	$P < 0.001$	
				Δ daytime asthma symptom score	-0.13	-0.02	$P = 0.04$	
				Δ night awakenings (n/week)	-1.04	-0.45	$P = 0.01$	
				Asthma attacks (% patients)	6.2	12.0	$P = 0.06$	

Table 6: Summary of studies investigating the effect of pharmaceuticals (leukotriene antagonists versus leukotriene antagonists) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Dockhorn et al. 2000) CO Grade 1+ Country: United States	Montelukast po 10 mg V Montelukast IV 7 mg V Placebo 24 hours each	Inclusion: Age 15-56 yrs FEV_1 40-80%PV Current non-smoker (history < 7 pack-years) Exclusion: Pharmaceutical limitations	51		IV MNT	PO MNT	Diff in means (LS)[1]	95% CI	• Mean age 30 and female 44% • Mean FEV_1 64%PV • Pharmaceutical company producing montelukast funded and supported trial • Limited baseline data between initial randomised groups (FEV_1 comparison only) • 90% power to detect a 6.5% point difference in FEV_1 between montelukast groups • [1]LS = Least squares
				% Δ FEV_1 AUC (conc.time)	20.7	15.7	5.8	-0.41, 12.06	
				Rescue medication required (%)	18	24	N/A	*P* value *n.s.*	

Long-acting beta-agonists

Chronic asthma

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma

Study source, design and evidence grading	Intervention Comparison And study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Shrewsbury et al. 2000) MA Grade 1+	Salmeterol + inhaled steroids (Beclo-methasone 5 studies or fluticasone 4 studies) V At least doubling dose of inhaled steroids (Beclo-methasone 5 studies or fluticasone 4 studies) 12+ weeks	Inclusion: Age 12+ yrs RCT, double blind All languages Patients with symptomatic asthma, treated on current dose of inhaled steroids Search: 1985-1999 (September 1999 last search) MEDLINE, EMBASE, GlaxoWellcome databases	3685	Treatment with salmeterol plus inhaled steroids versus increased dose inhaled steroids (double+ dose) Mean difference (95% CI) in lung function	3 months	6 months	*P* value 3 months	*P* value 6 months	• 9 studies included • No evidence of heterogeneity between studies for PEFR and FEV_1 and exacerbation analysis. For symptoms and rescue comparison *P*<.10 in all cases. Comparison of 95% CI under fixed and random effects model cited by authors as small and clinically unimportant (data not provided) • Pharmaceutical company supported meta-analysis
				AM PEFR L/min	22.4 (15,30)	27.7 (19,38)	*P*<.001	*P*<.001	
				AM FEV_1 L	0.10 (0.04, 0.16)	0.08 (0.02,0.14)	*P*<.001	*P*<.01	
				Mean % difference (95% CI)					
				Days without symptoms	11% (8,15)	15%(11,19)	*P*<.001	*P*<.001	
				Nights without symptoms	5% (2,8)	6% (3,9)	*P*<.001	*P*<.001	
				Days without rescue treatment	16% (13,20)	19% (14,24)	*P*<.001	*P*<.001	
				Nights without rescue treatment	9% (5,12)	9% (5,13)	*P*<.001	*P*<.001	
				Difference (95% CI) in mean numbers of patients with exacerbation:					
				Any exacerbation	2.73 (0.43,5.04)		*P*=.02		
				Moderate/severe exacerbation	2.42 (0.24,4.60)		*P*=.03		

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Baraniuk et al. 1999) RCT Grade 1+ Country: United States	Fluticasone mdi 220 µg bd V Triamcinolone mdi 600 µg bd V Fluticasone mdi 88 µg bd + salmeterol mdi 42 µg bd 12 weeks	Inclusion: Age 12+ yrs FEV_1 40-65%PV Patients with FEV_1 65-85%PV 15+% increase in FEV_1 %PV after 30 min with 180 µg salbutamol BDP dosage 252-672 µg, or TAA 600-1000 µg, or FP 1000 µg daily 3+ months pre-study Exclusion: Smoker Serious asthma exacerbation previous 4 weeks	680	12 weeks (mean change cf. baseline) (se) AM FEV_1 (L) FEV_1 (L) %PV Symptom score % symptom-free days % rescue-free days Adverse event related to treatment (% patients) (mean change cf. baseline) (se) AM FEV_1 (L) FEV_1 (L) %PV Symptom score % symptom-free days % rescue-free days Adverse event related to treatment (% patients)	FP plus SLM 0.58 (0.03) 16.7 (1.0) -0.44(0.05) 29.2(2.9) 45.0(2.9) 14% FP 0.48(0.03) 14.0(0.6) -0.46(0.05) 22.6(2.6) 28.9(2.7) 13%	TAA 0.34 (0.03) 10.4 (0.80 -0.31(0.05) 11.9(2.1) 27.4(2,5) 8% TAA 0.34(0.03) 10.4(0.80 -0.31(0.05) 11.9(2.1) 27.4(2,5) 8%	*P* value *P*<.001 *P*≤.004 *P*≤.004 *P*≤.004 *P*≤.004 N/A *P* value *P*≤.027 *P*≤.035 *P*≤.035 *P*<.001 *n.s.* N/A	NNT NNH 17 NNT NNH 20	• Mean age 41 and female 59%, FEV_1 63%PV, non-white ethnicity 13% in FP + SLM group; mean age 40and female 61%, FEV_1 63%PV, non-white ethnicity 17% in FP group; mean age 39 and female 65%, FEV_1 63%PV, non-white ethnicity 11% in TAA group • No detail on randomisation method • Pharmaceutical company funded and supported trial

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes			Comments
(Aubier et al. 1999) RCT Grade 1+ Country: Netherlands, France	Combination: Fluticasone 500 µg + salmeterol 50 µg bd Diskus inh and placebo bd V Concurrent: Fluticasone 500 µg + salmeterol 50 µg bd Diskus inh and placebo bd V Fluticasone 500 µg bd diskus inh and placebo bd 12 weeks	Inclusion: Age 12-78 yrs ICS 12 weeks prior to run-in and BEC or BDP 1500-2000 µg or FP 750-1000 µg daily 4 weeks prior Symptomatic patients (score ≥2) Patients with FEV_1 50-100%PV PEFR 50-85%PV max PEFR after 15 min with 400 µg salbutamol	503	12 weeks (adj mean difference cf. baseline) (se) Relative to FP plus SLM combination. –ve values indicate higher overall value for combination therapy AM PEFR (l/min) *=90% CI **=95% CI PM PEFR (l/min) *=90% CI **=95% CI 28 weeks Adverse event related to treatment (% patients) Combination Concurrent FP alone	FP plus SLM concurrent -3 (4.3) -10, 4* *P*=.535 -6 (4.3) -13, 1* *P*=.160 17% 14% 19%	FP -21 (4.4) -29, -12** *P*<.001 -21 (4.3) -29, -12** *P*<.001	• Mean age 46 and female 43%, FEV_1 2.44L in FP + SLM combo group; mean age 48 and female 50%, FEV_1 2.32L in FP + SLM concurrent group; mean age 50 and female 47%, FEV_1 2.33L in FP group • Little detail on randomisation, concealment and blinding methodology • Post-randomization 100 patients withdrew, 19% of combo group, 16% of concurrent group and 25% from FP group • Pharmaceutical company funded and supported trial

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Condemi et al. 1999) RCT Grade 1+ Country: United States	Fluticasone mdi 88 µg bd + Salmeterol mdi 42 µg bd V Fluticasone mdi 220 µg bd 2-4 weeks pre-trial: Fluticasone 88 µg bd and as needed salbutamol Treatment 24 weeks	Inclusion: Age 12-75 yrs FEV_1 40-65%PV or 65-85%PV plus one or more of: ≥4 puffs salbutamol daily, 2 days AM/PM PEFR variance ≥20%, 2+ nights asthma awakenings, 2+ days symptom score ≥2 Exclusion: Current tobacco use Hospital asthma admission previous month	437	24 weeks (cf. baseline) (se) (Change)	FP plus SLM	FP	*P* value	• Mean age 37 and female 62%, FEV_1 2.12L in FP + SLM group; mean age 37and female 60%, FEV_1 2.14L in FP group • No detail on randomisation methodology • Pharmaceutical company funded and supported trial • Study drop out rate 9% in FP + SLM group 14% in FP group
				AM PEFR L/min	+46.5(3.5)	+23.8(3.2)	*P*<.001	
				FEV_1 (L)	0.43 (0.04)	0.33 (0.03)	*P*=.013	
				Symptom free days %	+26%	+10%	*P*<.001	
				Rescue salbutamol use (Mean no. puffs daily)	-2.51(0.17)	-1.55(0.15)	*P*<.001	

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kavuru et al. 2000) RCT Grade 1+ Country: United States	Fluticasone 100 µg plus salmeterol 50 µg bd Diskus inh V Salmeterol 50 µg bd Diskus inh V Fluticasone 100 µg bd Diskus inh V Placebo inh bd 12 weeks	Inclusion: Age 12-70 yrs Patients with FEV_1 40-85%PV and ±15% of the screening FEV_1 Either ICS previous 12 weeks and dose (either BDP 252-420µg daily,TAA 600-1000 µg daily, FP 176 µg daily) previous 4 weeks OR SLM 1+ weeks prior Exclusion: ICS group and 12+ puffs salbutamol daily for 3+ days or SLM group 6+ puffs daily or 3+ days 3+ nighttime awakenings previous 7 days req salbutamol Smoker previous 12 months >10 pack years smoker	356	12 weeks (cf. baseline) FEV_1 (L) mean change (se) Asthma symptom score mean change (se) % days no symptoms mean change (se) Adverse event related to treatment (% patients) (cf. baseline) FEV_1 (L) mean change (se) Asthma symptom score Mean change (se) % days no symptoms mean change (se) Adverse event related to treatment (% patients) (cf. baseline) FEV_1 (L) mean change (se) Asthma symptom score Mean change (se) % days no symptoms mean change (se) Adverse event related to treatment (% patients)	FP plus SLM 0.51(0.05) -0.7(0.11) 22.6(4.59) 3% FP plus SLM 0.51(0.05) -0.7(0.11) 22.6(4.59) 3% FP plus SLM 0.51(0.05) -0.7(0.11) 22.6(4.59) 3%	SLM 0.11(0.06) -0.1(0.1) 8.0(3.29) 35% FP 0.28(0.05) -0.2(0.09) 7.2(4.09) 11% Placebo 0.01(0.07) 0.4(0.10) -3.8(3.01) 49%	*P* Value *P*≤.013 *P*≤.013 *P*≤.013 N/A *P*<.001 *P*≤.025 *P*≤.025 N/A *P*≤.027 *P*≤.013 *P*≤.013 N/A	• Mean age 38 and female 41%, no completing study 83% in FP + SLM group; mean age 37 and female 49%, completion rate 56% in SLM group; mean age 39 and female 48%, completion rate 74% in FP group; mean age 35 and female 49%, completion rate 34% in placebo group • Post-randomization, 21 patients from one site excluded because of poor practice standards. ITT analysis excludes these, small difference (non-quantified) in results if included. • Pharmaceutical company funded and supported trial

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(van Noord et al. 1999) RCT Grade 1- Country: Netherlands	Low steroid requirement: Fluticasone inh (100 µg bd open) + Fluticasone inh (100 µg bd blind) OR Fluticasone inh (100 µg bd open) + Salmeterol inh (50 µg bd blind) V High steroid requirement: Fluticasone inh (250 µg bd open) + Fluticasone inh (250 µg bd blind) OR Fluticasone inh (250 µg bd open) + Salmeterol inh (50 µg bd blind) Run in: 4 weeks Treatment: 12 weeks	Inclusion: Age 12-75 yrs $FEV_1 \geq 50\%PV$ 10+% increase in FEV_1 PV with 400µg salbutamol mdi or 800 µg inh (3 visits or pre-run in period 4 weeks) Daily symptom score ≥1, or diurnal var in PEFR 15+%, or rescue salbutamol 2+ times daily on 4/14 days run in period Exclusion: Change in asthma medication previous 6 weeks OCS previous 3 months	274	12 weeks PEFR L/min (mean increase cf. baseline) (se) AM PM FEV_1 (L) visit 4 (4 weeks) visit 5 (12 weeks) Odds Ratios (FP high dose plus SLM relative to FP low dose plus SLM) Rescue salbutamol use Day Night Days with symptoms	FP low dose plus SLM +18.6 (3.8) +16.2 (4.0) 2.53 (0.8) 2.47 (0.8)	FP High dose plus SLM N/A N/A 2.45 (0.8) 2.48 (0.9) 1.47 2.19 1.52	*P* value *P*<.001 *P*<.001 *P*=.04 *P*=.18 *P*=.03 *P*<.001 *P*=.04	• Mean age 46 and female 53%, FEV_1 (mean L) 2.33 in FP low dose + SLM group; mean age 47 and female 51%, FEV_1 (mean L) 2.34 in FP high dose group • High and low steroid requirements determined pre-study and at run-in • No detail on randomisation, blinding and concealment methodology • Intention to treat based analysis not evident. Study drop out rate 4% in FP low dose + SLM group 7% in FP high dose group • Several key study results lack data detail • Pharmaceutical company funded and supported trial

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Jenkins et al. 2000) RCT Grade 1+ Country: 9 countries	Salmeterol disk inh 50 µg + Fluticasone disk inh 250 µg + placebo turb inh bd V Budesonide turb inh 800 µg + placebo disk inh bd 24 weeks	Inclusion: Age 14-80 yrs 4+ weeks pre-study: FEV_1 or PEFR≥ 50-85%PV 15+% increase in FEV_1 or mean AM PEFR≤85% after β-agonist Salbutamol 2+ times daily 2+ daytime symptom score on 4+/7 days Exclusion: Asthma requiring hospitalization previous 4 weeks Smoker ≥10 pack years smoker	353	24 weeks adjusted mean over treatment period (se)	FP plus SLM	BDP	*P* value	NNT	• Mean age 45 and female 50%, FEV_1 (mean% PV) 68 in FP + SLM group; mean age 48 and female 50%, FEV_1 (mean% PV) 72 in BDP group • International based study (9 countries) • Little detail on randomisation, blinding and concealment methodology • Pharmaceutical company funded and supported trial
				AM PEFR L/min	406 (3.67)	380 (3.81)	*P*<.001		
				PM	416 (3.14)	398 (3.25)	*P*<.001		
				Median % symptom-free days	60%	34%	*P*≤.001	4 NNH	
				Adverse events related to treatment (% patients)	14%	19%	N/A	20	

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Pearlman et al. 1999) RCT Grade 1- Country: United States	Placebo mdi bd V Salmeterol mdi 42 µg bd V Fluticasone mdi 88 µg bd V Fluticasone mdi 220 µg bd V Salmeterol mdi 42 µg bd + Fluticasone mdi 88 µg bd V Salmeterol mdi 42 µg bd + Fluticasone mdi 220 µg bd 4 weeks	Inclusion: Age 12-62 yrs FEV_1 50-80%PV 15+% increase in FEV_1 15 min after 180 µg (2 puffs) salbutamol Daily or as needed β-agonists previous 6 months Exclusion: Smoker previous 12 months >10 pack years O/I/IVCS previous 1 month Daily OCS previous 6 months	136	4 weeks	Baseline FEV_1 (L)	Endpoint mean change FEV_1 (L)	*P* value	• Poor comparative baseline demographics between groups • Placebo N=23, mean age 35 and female 57%, Non-Caucasian 9% • SLM (42µg) N=21, mean age 29 and female 33%, Non-Caucasian 0% • FP (88µg) N=23, mean age 27 and female 26%, Non-Caucasian 0%, • FP (220µg), N=23, mean age 32 and female 43%, Non-Caucasian 9% • SLM (42µg) + FP (88µg) N=25, mean age 33 and female 60%, Non-Caucasian 16% • SLM (42µg) + FP (220µg) N=21, mean age 26 and female 33%, Non-Caucasian 19% • Pharmaceutical company funded and supported trial • Study drop out rate 4% in FP low dose + SLM group, 7% in FP high dose group • Several key study results lack data detail
				Placebo	2.39 (0.13)	0 (0.09)		
				SLM (42µg)	2.75 (0.1)	0.29 (0.12)		
				FP (88µg)	2.91 (0.13)	0.27 (0.07)		
				FP (220µg),	2.52 (0.14)	0.30 (0.09)	*P*≤.05*	
				SLM (42µg) + FP (88µg)	2.31 (0.12)	0.59 (0.10)	*P*<.05*^	
				SLM (42µg) + FP (220µg)	2.62 (0.12)	0.75 (0.16)	*P*<.05*^	
				* vs placebo ^ vs SLM 42µg, FP 88µg and FP220µg				
					Baseline	Mean change		
				Asthma symptom score Placebo				
				SLM (42µg)	1.3 (0.2)	-0.2 (0.2)		
				FP (88µg)	1.3 (0.2)	-0.5 (0.1)		
				FP (220µg),	1.2 (0.1)	-0.1 (0.1)	*P*<.05*	
				SLM (42µg) + FP (88µg)	1.3 (0.2)	-0.3 (0.1)		
				SLM (42µg) + FP (220µg)	1.2 (0.2)	-0.8 (0.2)		
					1.1 (0.2)	-0.4 (0.1)	*P*<.05*^	
				* vs placebo ^ vs FP 88µg				

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Weersink et al. 1997) RCT Grade 1- Country: Netherlands	Salmeterol mdi 50 µg bd V Fluticasone mdi 250 µg bd V Fluticasone mdi 250 µg bd + salmeterol mdi 50 µg bd Methacholine challenge (MCh) Or Adenosine 5'mono-phosphate challenge (AMP) To FEV_1 PC_{20} or MCh (19.6mg/ml) or AMP (640mg/ml) 6 weeks	<u>Inclusion:</u> Age 18-45 yrs Circadian variation in PEFR15+% BHR to MCh PC_{20} <9.6 mg/ml IgE elevated to house dust mite (RAST≥2) Short-acting β-agonist on demand previous 4 weeks <u>Exclusion:</u> Smoker Acute asthma exacerbation, OCS previous 8 weeks ICS previous 4 weeks	50	6 weeks Mean Circadian PEFR variation 100*(highest-lowest 24-h value)/mean 24-h value per day over 3 days Baseline End of period FEV_1 (L) (%PV increase cf. baseline) 4 PM (se) 4 AM (se) PC_{20} MCh (se) 4 PM 4 AM	<u>SLM</u> 22.4% 9.1% +10.8% (2.4) +19.6% (3.6) +1.5(0.5) +2.4(0.5)	<u>FP</u> 24.0% 7.9% +7.6% (3.4) +15.9% (3.0) +2.1(0.5) +3.0(0.5)	<u>SLM+FP</u> 24% 10% +5.9% (3.8) +17.9% (3.8) 2.5(0.6) 2.9(0.8)	<u>*P Value*</u> Between *n.s.* Within *P*<.0001 Between *P*=.2 Within *P*=.0001 Between times *P*=.0005 PC_{20} MCh Between *P*=.04 Within *P*<.0001Between times *P*=.1	• Mean age 28 and female 50%, FEV_1 77%PV, in SLM group; mean age 28 and female 56%, FEV_1 88%PV, in FP group; mean age 26 and female 50%, FEV_1 83%PV, SLM + FP group • Baseline differences post-randomisation • Patients recruited from 1 outpatient clinic and newspaper advertisements • No intention to treat analysis, 4 treated patients not included in analysis • Pharmaceutical company funded and supported trial

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Murray et al. 1999) RCT Grade 1+ Country: United States	Beclomethasone mdi 168 µg bd + salmeterol mdi 42 µg bd V Beclomethasone mdi 336 µg bd 24 weeks	Inclusion: Age 18-82 yrs FEV_1 45-80%PV 12+% increase in FEV_1 PV with 180 µg salbutamol Symptomatic while taking 336 µg beclomethsone or 800 µg triamcinolone daily Constant immunotherapy ok if 12+ weeks Exclusion: Patients on other asthma medication except theophylline, as needed salbutamol and asthma exacerbation medication	514	24 weeks	BDP + SLM	BDP	*P* value	• Mean age 42 and female 59%, FEV_1 65%PV in BDP + SLM group; mean age 42 and female 55%, FEV_1 64%PV in BDP dose group • Pharmaceutical company funded and supported trial • Several key study results (salbutamol use, drug safety) lack data detail • Unclear if intention to treat analysis used
				FEV_1 (L) baseline	2.30	2.31		
				24 weeks (cf. BDP)	2.68	2.54	*P*<.05	
				Symptom score (mean change cf. baseline at 24 weeks)				
				Wheeze	-0.49	-0.27	*P*≤.05	
				Shortness of breath	-0.71	-0.25	*P*≤.05	
				Chest tightness	-0.62	-0.33	*P*≤.05	
				Asthma exacerbations % patients	17%	18%	*n.s.*	

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Kelsen et al. 1999) RCT Grade 1+ Country: United States	Beclomethasone mdi 168 µg bd + Salmeterol mdi 42 µg bd V Beclomethsone mdi 336 µg bd Run-in: 2 weeks Treatment: 24 weeks	Inclusion: Age 18-77 yrs FEV_1 45%-80%PV ≥12% increase in FEV_1 after 180 µg salbutamol ≥3/7 days symptoms, rescue medication in previous week ICS 336 µg daily BDP or 800 µg daily 2 weeks prior Non-smoker	483	24 weeks (mean change over treatment period)	BEC+ SLM	BEC	*P* value	NNT	• Mean age 42 and female 57%, FEV_1 65%PV in BEC+SLM group; mean age 42 and female 65%, FEV_1 64%PV in BEC group • Of the 483 patients randomized 20.1% did not complete study. Dropout rates 20% in each treatment arm. Results use ITT based analysis • Some primary PEFR data values are not reported, only *p* values given • Pharmaceutical company funded and supported trial
				Mean AM PEFR L/min					
				Baseline L/min	389.7	390			
				Treatment period L/min	N/A	N/A	*P*<.001		
				Mean PM PEFR L/min					
				Baseline L/min	N/A	N/A			
				Treatment period L/min	37.5	14.8	*P*<.001		
				% of symptom free days	23.6%	12.5%	*P*≤.05	9	
				Mean change over 24 weeks (se)					
				% nights with no awakenings					
				(baseline) (se)	67.0 (2.3)	68.0 (2.2)	N/A		
				mean change	18.8 (1.7)	13.4 (1.6)	*P*≤.05		
				% nights no salbutamol use					
				baseline (se)	60.2 (2.5)	60.4 (2.4)	N/A		
				mean change	23.2 (2.0)	14.7 (1.9)	*P*≤.05		
				n and % patients reporting exacerbations	38 (16%)	44 (18%)	N/A		
				n and % patients with drug related adverse events	26 (11%)	34 (14%)	N/A		

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Nathan et al. 1999) RCT Grade 1+ Country: United States	Salmeterol mdi 42 µg bd V Beclomethasone mdi 84 µg Qid V Placebo mdi bd Methacholine challenge (MCh) To FEV_1 PC_{20} or MCh 75 (mg/ml) in neb 26 weeks	Inclusion: Age 12+ yrs FEV_1 65-90%PV 12+% increase in FEV_1 within 30 min of 180 µg salbutamol mdi Daily/as needed β-agonists with no I/OCS previous 6 months Exclusion: Decline in FEV_1 of ≥ 15% after saline inhalation Asthma requiring hospitalization previous 4 weeks	386	26 weeks mean increase (se) over treatment period FEV_1 (L) Salbutamol free nights (mean % increase) Mean increase PD_{20} MCh (se) Week 14 Week 26	SLM 0.28 (0.04) 23% 1.39 (0.24) 1.29 (0.26)	BEC 0.23 (0.04) 23% 1.57 (0.26) 1.42 (0.24)	Placebo 0.08 (0.04) 9% 0.16 (0.22) 0.24 (0.29)	*P* value cf. placebo *P*≤.014 *P*≤.014 *P*<.001 *P*≤.033	• Mean age 31 and female 54%, FEV_1 79%PV, AM PEFR(L/min) 405 in SLM group; mean age 30 and female 57%, FEV_1 78%PV, PEFR(L/min) 394 in BDP group; mean age 29 and female 50%, FEV_1 81%PV, PEFR(L/min) 417 in placebo group • Significantly higher baseline AM PEFR in placebo group • ITT analysis but 81/368 (22%) withdrawals. Across treatment arms 23% SLM, 18% BEC, 22% PLC groups • Data for some primary outcomes not shown • Pharmaceutical company funded and supported trial

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Vermetten et al. 1999) RCT Grade 1- Country: Netherlands	Beclomethasone D-inh 200 µg bd + Salmeterol D-inh 50 µg bd V Beclomethasone diskinh 400 µg bd Run-in: 2 weeks Treatment: 12 weeks	Inclusion: Age 18-66 yrs 6+ weeks prior: ICS BEC/BDP 200-400 µg daily ≥15% reversibility in PEF Exclusion: Asthma exacerbation requiring change to medication in run-in period	233	12 weeks (average of last 2 weeks of treatment period)	BEC+ SLM	BEC	*P* value	• Mean age 42 and female 47%, AM PEFR(l/min) 404, PM PEFR 431 in BEC+SLM group; mean age 42 and female 62%, AM PEFR(l/min) 390, PM PEFR 413 in BEC group • Differences in baseline demographics for % female and AM/PM PEFR values • Of the 233 patients randomized 202 completed study. Whether or not ITT analysis not specified. No detail on randomisation, blinding and concealment methodology. • Treatment endpoints are averages over the last 2 weeks. • Some primary PEFR data values are not reported, only *p* values given • Pharmaceutical company supported trial
				Mean AM PEFR L/min				
				Baseline L/min	404	390		
				Treatment period L/min	N/A	N/A	*P*=.066	
				Mean PM PEFR L/min				
				Baseline L/min	431	413		
				Treatment period L/min	N/A	N/A	*P*=.036	
				Diurnal variation in PEFR%(se)				
				Baseline	9.5% (0.8)	8.8% (0.6)		
				Treatment period	6.6% (0.6)	7.2% (0.7)	*n.s.*	
				(proportion of days with) Asthma symptoms				
				Day Baseline period	0.56 (0.04)	0.54 (0.03)		
				Day Treatment period	0.37 (0.04)	0.38 (0.04)	*n.s.*	
				Night Baseline period	0.43 (0.04)	0.41 (0.03)		
				Night Treatment period	0.33 (0.04)	0.34 (0.04)	*n.s.*	
				Av. No. of blisters per day of rescue medication-baseline	0.88 (0.09)	0.84 (0.09)		
				Treatment	0.48 (0.07)	0.61 (0.10)	*P*<0.05	
				Av. No. of blisters per night of rescue medication-baseline	0.47 (0.06)	0.47 (0.05)		
				Treatment	0.30 (0.06)	0.37 (0.06)	*n.s.*	

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Pauwels et al. 1997) RCT Grade 1+ Country: 9 countries	Run-in period: Budesonide inh 800 µg bd terbutaline 250 µg inh as needed Treatment: Budesonide inh 100 µg bd + placebo inh bd V Budesonide 100 µg inh bd + formoterol inh 12 µg bd V Budesonide inh 400 µg bd + placebo inh bd V Budesonide 400 µg inh bd + formoterol inh 12 µg bd terbutaline 250 µg inh rescue medication Run-in: 4 weeks Treatment: 52 weeks	Inclusion: Age 18-70 yrs Patients with $FEV_1 \geq 50\%$PV and 15+% increase from baseline FEV_1 after inhalation of 1 mg terbutaline Exclusion: Patients taking 2000+ µg daily beclomethasone or 1600+ µg daily mdi or 800+ µg daily budesonide inh 3+ courses OCS or asthma requiring hospitalization previous 6 months	852	52 weeks	Low dose BDP + placebo	Low dose BDP + FRM	High dose BDP + placebo	High dose BDP+ FRM	• Mean age 42 and female 49%, FEV_1 76 in low BDP + placebo group; mean age 41 and female 50%, FEV_1 76 in low BUD + FRM group; mean age 44 and female 52%, FEV_1 76 in high BDP + placebo group; mean age 42 and female 53%, FEV_1 76%PV high BUD + FRM group • International based study (9 countries) • Post-randomisation, 158 patients did not complete study, 44 of these did not fulfil the entry criteria and were incorrectly randomised. Whether ITT analysis not clearly defined • Pharmaceutical company funded and supported trial
				Yearly rate of asthma exacerbations (no/patient/yr)					
				Severe	0.91	0.67	0.46	0.34	
				Mild	35.4	21.3	22.3	13.4	
				Episode free days (mean % of year)	41.7%	51.1%	45.7%	54.8%	
				Asthma symptom score Day	0.57	0.46	0.53	0.33	
				Night	0.37	0.31	0.38	0.20	
				Rescue medication during day no of inhalations	0.91	0.57	0.82	0.44	
						*P V*alue Higher vs lower dose of BDP			
				Yearly rate of asthma exacerbations (no/patient/yr)					
				Severe		*P*<.001			
				Mild		*P*<.001			
				Episode free days (mean % of year)		*P*=.16			
				Asthma symptom score					
				Day		*P*=.01			
				Night		*P*=.01			
				Rescue medication during day (no of inhalations)		*P*<.001			

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Juniper et al. 1999) RCT Grade 1- Country: 5 countries	Run-in period: Budesonide inh 800 µg bd terbutaline 250 µg inh as needed Treatment: Budesonide inh 100 µg bd + placebo inh bd V Budesonide 100 µg inh bd + formoterol inh 12 µg bd V Budesonide inh 400 µg bd + placebo inh bd V Budesonide 400 µg inh bd + formoterol inh 12 µg bd Terbutaline 250 µg inh rescue medication Run-in: 4 weeks Treatment: 52 weeks	Inclusion: Age 18-70 yrs Patients with $FEV_1 \geq 50\%PV$ and 15+% increase from baseline FEV_1 after inhalation of 1 mg terbutaline IGS previous 3+ months with patients taking <2000 µg daily beclomethasone or <1600 µg daily mdi or <800 µg daily budesonide inh	470	52 weeks	High dose BDP+ FRM	*P* Value Cf. other groups	NNT (provided Result)	• Mean age 42 and female 51% in low BDP + placebo group; mean age 42 and female 48% in low BDP + FRM group; mean age 44 and female 51% in high BDP + placebo group; mean age 44 and female 59% in high BDP + FRM group • International based study (9 countries) • Earlier study acknowledgement to (Pauwels et al. 1997) This study's primary outcome measure is asthma quality of life assessment using AQLQ. Clinical results previously reported in earlier study • Post-randomisation, 114/470 (24%) of patients did not complete study after 52 weeks. 4/470 patients did not fill in AQLQ at baseline are excluded from analysis • Insufficient data detail for analysis of AQLQ results • Pharmaceutical company funded and supported trial
				AQLQ total score change	0.21	*P*=.028	11.9	

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kips et al. 2000) RCT Grade 1- Country: Canada, England, Belgium	Run-in period: Budesonide inh 800 µg bd terbutaline 0.25 mg inh as needed Budesonide 100 µg inh bd + formoterol inh 12 µg bd V Budesonide inh 400 µg bd + placebo inh bd Run-in: 4 weeks Treatment: 52 weeks	Inclusion: Age 18-70 yrs Patients with $FEV_1 \geq 50\%$PV and 15+% increase from baseline FEV_1 after inhalation of 1 mg terbutaline Exclusion: Patients taking 2000+ µg daily beclomethasone or 1600+ µg daily mdi or 800+ µg daily budesonide inh or 800+ µg daily fluticasone inh 3+ course OCS or asthma requiring hospitalization previous 6 months	60	52 weeks	BDP + FRM	BDP + placebo	*P* value	• Mean age 35 and female 59%, ICS µg daily 676, FEV_1 L start run-in 2.87, end run-in 2.93 in BDP + FRM group; mean age 38 and female 61%, ICS µg daily 706.5, FEV_1 L start run-in 2.52, end run-in 2.71 in BDP + placebo group • Differences in baseline FEV_1 (lower in BDP+ placebo group), ICS usage higher here also. Not significant according to study • International based study (3 countries) • Primary efficacy outcome markers of airway inflammation in induced sputum. Only secondary outcomes appraised. Lung function data detail not reported • Whether ITT analysis not clearly defined. No information on study drop out rates during treatment • Pharmaceutical company funded and supported trial
				Yearly rate of asthma exacerbations (no/patient/yr)				
				Severe (se)	0.29 (0.14)	0.47 (0.24)	*n.s.*	
				Mild (se)	18.3 (6.92)	14.6 (5.42)	*n.s.*	
				Episode free days (mean % of year) (se)	41.3% (7.0)	30.4% (6.0)	*n.s.* *n.s.*	
				Mean AM PEFR L/min	N/A	N/A	*n.s.*	
				Mean PM L/min	N/A	N/A	*P*<.05	

Table 7: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Crompton et al. 1999) RCT Grade 1+ Country: 3 European countries	Bambuterol po 10 mg nocte (1 week) 20 mg nocte (5 weeks) + placebo mdi V Salmeterol mdi 50 µg bd + placebo Run-in: 2 weeks Treatment: 6 weeks	Inclusion: Age 18+ yrs 4+ weeks prior: ICS BDP/BEC 800-2000 µg daily other than with turbuhaler or FP/BUD 400-2000 µg daily via turbuhaler or OCS such as prednisone at ≤ 20 mg daily ≥1 nocturnal/early morning awakening req rescue medication ≥15% decr in overnight PEFR on 3/7 days preceding entry Exclusion: Asthma requiring hospitalization Previous 4 weeks	135	6 weeks Median AM PEFR L/min	BMB	SLM	*P* value	• Mean age 41 and female 60%, FEV_1 66%PV in BMB group; mean age 41 and female 56%, FEV_1 68%PV in SLM group • International based study (3 countries) • Of the 135 patients randomized 118 completed study. Of the total, 126 patients were considered valid and are included in the analysis. Not strict ITT analysis • Treatment endpoints are calculated during weeks 3 to 6 Both median and mean values calculated and appropriate statistical measures used • Pharmaceutical company funded and supported trial
				Baseline L/min	276	272	N/A	
				Treatment period L/min	310	327	N/A	
				Change from baseline	50	55	*P*=.53	
				Median change (cf. baseline)				
				Evening PEFR L/min	12	3	*P*=.82	
				Percent overnight fall in PEFR%	-11%	-14%	*P*=.17	
				Percent nights an awakening %	-21%	-29%	*P*=.22	
				No. puffs rescue medication during day	-0.33	-0.57	*P*=.24	
				No. puffs rescue medication during night	-0.28	-0.26	*P*=.88	
				Asthma symptoms, day	-0.17	-0.11	*P*=.48	
				night	-0.32	-0.32	*P*=.57	

Table 8: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus theophylline) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Pollard et al. 1997) RCT Grade 1+ Country: United States	Salmeterol mdi (42 µg bd) V Theophylline po (Individual dose titrated slo-bd) V Placebo Inh and po 12 weeks	Inclusion: Age 12+ yrs FEV_1 > 50%PV 15+% increase in FEV_1 with salbutamol inh Exclusion: Other bronchodilators	484	12 weeks Mean change AM PEFR(cf. baseline) (L/min) Mean change (cf. baseline) Nighttime awakenings/wk Asthma symptom score Salbutamol use puffs/day Drug related adverse event	SLM +10.3 -0.7 -0.11 -1.1 9%	THP -4.5 -0.1 0.01 0.06 19%	*P* value *P*≤.02 *P*<.02 *P*<.02 *P*<.02 *P*<.05	• Mean age 31 and female 52% in salmeterol group; mean age 30 and 54% in theophylline group • 54% patients on concurrent ICS therapy • Pharmaceutical company funded and supported trial • Combined results of two identical trials

Table 8: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus theophylline) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention Comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Nutini et al. 1998) RCT Grade 1- Country: Italy	Salmeterol inh 50 µg bd V Theophylline po 50 dose titrated bd 12 weeks (drug efficacy) 52 weeks (drug safety)	Inclusion: Age 18+ yrs FEV_1 50-80%PV 15+% increase in FEV_1 with 200 µg salbutamol inh Exclusion: Variable smoking history Asthma requiring emergency care – past month	112	12 weeks Symptom free Days Nights Days with no rescue medication use Days Nights QOL index score Adverse drug events	SLM 65.7% 65.7% 68.7% 70.1% 9.7 9	THP 56.8% 60.2% 57.2% 63.0% 8.6 18	*P* value *P*<.005 *P*<.01 *P*<.001 *P*<.001 N/A N/A	NNT 11 18 9 14	• Mean age 46 and female 44%, mean FEV_1 (L) 2.21 in SLM group; mean age 48 and 32% and mean FEV_1 (L) 2.10 in THP group • Pharmaceutical company funded and supported trial • Open study design • Intention to treat analysis

Table 9: Smmary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kemp et al. 1998) RCT Grade 1+ Country: United States	Salmeterol inh (breath activated device) 50 µg bd + placebo mdi Qid V Salbutamol mdi 180 mg Qid + placebo mdi bd V Placebo mdi Qid 12 weeks	Inclusion: Age 18-79 yrs FEV_1 50-80%PV $FEV_1 \geq$ +15% after 30 minutes inh of 180 µg salbutamol Exclusion: Smoker	451		SLM	SLB	*P* value	• Mean age 31 and female 39%, FEV_1 65%PV, %race non-white 3% in SLM group; mean age 31 and female 43%, FEV_1 66%PV, race non-white 12% in SLB group; mean age 31 and female 43%, FEV_1 65%PV, race non-white 9% in PLC group • Significant difference in ethnic mix across groups • Unchanged ICS or cromolyn usage previous 3 months • All patients on "as needed" salbutamol use • Two identically designed trials with pooled data results • Unclear if intention to treat methodology used and number of patients included in analysis • Pharmaceutical company funded and supported trial
				Mean Area Under Curve AUC for FEV_1 (L/hrs)				
				Day 1	5.5	4.6		
				Week 12	6.1	3.4	*P*<.001	
				(12-hour serial pulmonary function testing)				
				Mean FEV_1 %PV from				
				Day 1	81%	85%		
				Week 12	84%	82%	*P*<.001	
				Treatment related adverse events % of patients	10%	9%	N/A	
				Baseline v Weeks 1-12				
				Mean % of nights without awakening (se)	63 (2.9) 85 (1.9)	68 (2.7) 71 (2.5)	*P*<.001	
				Mean asthma symptoms score	1.2 (0.07) 0.8 (0.06)	1.0 (0.06) 0.9 (0.05)	*P*<.01	
				Mean puff/d of rescue salbutamol use	4.3 (0.2) 1.6 (0.2)	4.3 (0.2) 2.2 (0.2)	*n.s.*	

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Boulet et al. 1997) RCT Grade 1+ Country: Canada	Salmeterol inh 50 µg bd V Salbutamol mdi 200 µg Qid 12 weeks	Inclusion: Age 12-76 yrs FEV_1 50-80%PV $FEV_1 \geq 15\%$ 15 minutes after inh of 200 µg salbutamol Exclusion: Other β-agonists and OCS ICS, IMM for at least 1 month pre-study	228		SLM	SLB	*P* value	NNT	• Mean age 37 and female 44%, FEV_1 66%PV in SLM group; age 40 and female 43%, FEV_1 66%PV in SBM group • Unclear if intention to treat methodology • Inadequate data results reported for appraisal of primary FEV_1 measure of efficacy • Pharmaceutical company funded trial
				Between treatment groups: Mean improvement over baseline FEV_1 AM postdose time point					
				3-6 hours	N/A	N/A	*P*<.001		
				10-12 hours	N/A	N/A	*P*≤.012		
				(day1, weeks 4, 8, 10, 12)					
				Mean post-dose changes in FEV_1 %	8.1%	9.7%	N/A		
				Mean improvement in AM PEFR(l/min)	35	-3	*P*<.001		
				% days no symptoms	29%	15%	*P*=.012	7	
				% nights no awakenings	14%	-1%	*P*<.001	7	

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Martin et al. 1999) CO Grade 1+ Country: United States	Salbutamol po (extended release) 4mg AM, 8 mg PM bd V Salmeterol inh 42 µg bd Treatment period(s) 3 weeks each 7-9 day washout	Inclusion: Age 18-65 yrs FEV_1 50-80%PV FEV_1 > 12% after inh salbutamol Stable asthma for previous 30 days Exclusion: Systemic CS β-agonists other than rescue salbutamol Theophylline (sustained release)	47		SLM	SLB	*P* value	NNT	• Mean age 35 and female 48%, FEV_1 67%PV, 61% of patients on ICS pre-study, 27% tobacco use history. • No baseline demographics for randomized treatment groups • Nocturnal asthma defined as ≥ 15% decrease in AM and night FEV_1 on 3/7 nights prior to randomization • 46/47 patients included in analysis, 1 lost to follow-up • Pharmaceutical company funded and supported trial
				Adjusted means					
				FEV_1 (l)	2.70	2.71	*n.s.*.		
				PEFR L/min AM	420	414	n.s.		
				% overnight change PEF	-7.9	-7.2	*n.s.*.		
				% overnight change FEV_1	-5.1	-4.0	*n.s.*.		
				Rescue salbutamol (no. of inhalations/day)	2.20	2.98	*P*=.001		
				% of no nighttime awakenings	84.6%	79.4%	*P*=.021	22	

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Ekstrom et al. 1998b) RCT Grade 1+ Country: 3 Scandinavian countries	Formoterol inh 12 µg (delivered dose 9 µg) bd + placebo V Terbutaline inh 0.5 mg Qid V Placebo inh Qid 12 weeks	Inclusion: Age 18-82 yrs FEV_1 50-80%PV $FEV_1 \geq 15\%$ 15 minutes after inh of 0.5 mg turbutaline	343		FRM vs placebo	FRM vs TEB	TEB vs Placebo	• Mean age 49 and female 49%, FEV_1 62%PV , current/past smoker 62% in SLM group; mean age 48 and female 59%, FEV_1 61%PV, current/ex smoker 57% in TEB group; mean age 47 and female 49%, FEV_1 60%PV, current/ex-smoker 63% in PLC group • 89% of patients on ICS pre-study. Patients allowed to use ICS and terbutaline as rescue medication • International based study (3 countries) • Unclear if intention to treat methodology • Pharmaceutical company funded and supported trial
				Mean difference in improvement over baseline				
				PEFR L/min AM	14.6	21.9	-7.2	
				PM	16.2	16.7	-0.6	
				Asthma symptoms – night	-0.20	-0.16	-.0.05	
				Rescue medication (no. of inhalations)				
				Day	-0.53	-0.10	-0.43	
				Night	-0.67	-0.11	-0.56	
				P value				
				PEFR L/min AM	*P*=.0022	*P*=.0001	*n.s.*.	
				PM	*P*=.0001	*P*=.0001	n.s.	
				Asthma symptoms – night	*P*=.0025	*P*=.019	n.s	
				Rescue medication (no. of inhalations)				
				Day	*P*=.013	*n.s.*.	*P*=.043	
				Night	*P*=.0042	n.s.	*P*=.015	

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Lipworth et al. 1998) RCT Grade 1+ Country: Scotland	Formoterol inh 6 µg (delivered dose 4.5 µg) bd + placebo V Formoterol inh 24 µg (delivered dose 9 µg -2 puffs) bd + placebo V Formoterol inh 12 µg daily (delivered dose 9 µg) + placebo V Terbutaline inh 500 mg Qid V Placebo inh Qid Methacholine challenge (MCh) 3.125 µg - 6400 µg to FEV_1 PD_{20} 2 weeks	Inclusion: Age 16-65 yrs $FEV_1 \geq 60\%PV$ PD_{20} (MCh) ≤1000 µg Constant dosage of ICS ≤2000 µg BUD, BDP or FP Exclusion: Patients on OCS previous 4 weeks Smoker previous 12 months	72	Methacholine protection ratios compared with placebo	Geometric Mean fold Protection Ratio	95% CI	*P* value	• Mean age 33 and female 47%, FEV_1 90%PV FRM 24 µg group; mean age 36 and female 53%, FEV_1 87%PV in FRM 12 µg group; mean age 39 and female 71%, FEV_1 85%PV in FRM 6 µg group; mean age 42 and female 50%, FEV_1 88%PV in TEB 500 µg group; mean age 38 and female 43%, FEV_1 86%PV in placebo group • Unclear if intention to treat methodology • Pharmaceutical company funded and supported trial
				Formoterol 24 µg bd				
				First dose	10.2	4.6 – 22.5	N/A	
				14 days	1.4	0.6 – 3.4	N/A	
				Formoterol 12 µg bd				
				First dose	6.4	2.9 – 14.1	N/A	
				14 days	1.5	0.6 – 3.8	N/A	
				Formoterol 6 µg bd				
				First dose	5.5	2.5 – 12.3	N/A	
				14 days	1.6	0.6 – 4.0	N/A	
				Terbutaline 500 µg Qid				
				First dose	3.4	1.5 – 7.8	N/A	
				14 days	1.9	0.8 – 4.9	N/A	
				Pre-challenge FEV_1 1 hour after use of medication After 14 days of treatment (as % ratio versus placebo)				
				Formoterol 24 µg bd	109%	103,116%	*n.s.*	
				Formoterol 12 µg bd	111%	105, 118%	*n.s.*	
				Formoterol 6 µg bd	109%	102, 115%	*n.s.*	
				Terbutaline 500 µg Qid	105%	99, 112%	*n.s.*	

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Seberova and Andersson 2000) CO Grade 1- Country: Czech Republic	5 study visits, with single doses: minimum 2 days washout Formoterol inh 4.5 µg or 9 µg V Salbutamol mdi 100 µg or 200 µg V Placebo	Inclusion: Age 18-64 yrs $FEV_1 \geq 40\%PV$ $FEV_1 \geq 1.51$ $FEV_1 \geq 15\%$ 15 minutes after inh of 0.5 mg terbutaline Exclusion: If FEV_1 not within ±12% of baseline FEV_1 patients asked to return another day Oral, inh long-acting β-agonists, GCS during study	36	FEV_1 at 3 minutes after inhalation	% Increase in FEV_1 (cf. baseline	*P* value cf. placebo		• Mean age 34 and % female unknown, mean FEV_1 (L) 2.75 • No baseline demographics for randomized treatment groups • Treatment period undefined • Randomized at each study visit • No power analysis for study sample size • Pharmaceutical company funded and supported trial
				Salbutamol 100 µg	+10.0%	*P*<.001	Between groups	
				Salbutamol 200 µg	+11.4%	*P*<.001		
				Formoterol 4.5 µg	+11.7%	*P*<.001		
				Formoterol 9.0 µg	+11.8%	*P*<.001	*n.s.*	

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Lipworth et al. 1999) RCT Grade 1- Country: Scotland	Formoterol inh 12 µg mane V Formoterol inh 6 µg bd V Formoterol inh 24 µg bd V Terbutaline inh 500 µg Qid 2 weeks	Inclusion: Age 18-45 yrs $FEV_1 \geq 60\%PV$ PD_{20} in FEV_1 response to methacholine challenge of 1000 µg and 2-doubling dose protection in response to a single test dose of formoterol inh 24 µg Non-smoker	38	Mean values	FRM 6 µg bd	FRM 12 µg daily	FRM 24 µg bd*	TEB 500 µg Qid	• N=8, mean age 39 and female 38%, FEV_1 80%PV in FRM 6 µg group; N=10, age 41 and female 40%, FEV_1 84%PV in FRM 12 µg group; N=11, age 32 and female 45%, FEV_1 91%PV in FRM 24 µg group; N=11, age 36 and female 44%, FEV_1 87%PV in TEB group • Small numbers in each treatment group, no significant demographic differences between groups • All patients on regular ICS therapy. On demand β-agonists • Unclear if intention to treat methodology • Results presented are only secondary outcome measures. Primary outcome bronchoprotective sensitivity • Pharmaceutical support in provision of inhalers for trial
				AM PEFR(L/min)(se) run-in	395 (55)	367 (44)	447 (30)	429 (46)	
				Treatment	415 (59)	391 (21)	490 (24)	428 (45)	
				PM PEFR(L/min)(se) run-in	398 (50)	417 (31)	471 (27)	435 (51)	
				Treatment	433 (59)	421 (25)	502 (24)	445 (46)	
				* *P*<.05 difference between run-in and treatment only in formoterol 24 µg bd group					

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study Source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Tattersfield 2001) RCT Grade 1+ Country: 4 European countries	As needed basis: Formoterol inh 4.5-54 µg daily V Terbutaline inh 0.5-6 µg daily 12 weeks	Inclusion: Age 18-75 yrs $FEV_1 \geq 50\%PV$ ICS mean dose 870 µg daily previous 4 weeks Requirement of β-agonists average 3/8 times during run-in period Exclusion: Patients inh 12+ rescue medication	362	Number at risk (remaining w/o severe asthma exacerbation) Days since randomization 0 20 40 60 80 Exacerbations: no. of patients/no. of exacerbations Need for OCS Mean difference in change over treatment (FRM-TEB) AM PEFR(L/min)(95% CI) PM PEFR(L/min)(95% CI) Diurnal variation % Symptom score – Day Night	FRM 182 173 165 153 146 26 / 29 21/26 (81%) 11 (3,20) 8 (0,15) -0.4 (-1.4,0.6) -0.04 -0.02	TEB 180 159 144 132 127 43 / 48 31/43 (72%)	*P* value *P*=.013 *P*=.009 *P*=.043 *P*=.44 *P*=.54 *P*=.68	• Mean age 46 and female 52%, FEV_1 74%PV in FRM group; mean age 48 and female 62%, FEV_1 74%PV in TEB group • Severe exacerbations defined by need for OCS or fall in PEFR of 30% from baseline on 2 consecutive days • International study (4 countries) • Pharmaceutical company funded and supported trial

Table 9: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study Source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Ekstrom et al. 1998a) RCT Grade 1- Country: 4 European countries	Formoterol inh 6 µg (delivered dose 4.5 µg) bd V Terbutaline inh 0.5 mg Qid V Placebo inh Qid 12 weeks	Inclusion: Age 18-79 yrs FEV_1 40-80%PV $FEV_1 \geq$ +15% and 200+ ml after inh of 0.5 mg terbutaline	397		FRM vs TEB	95%CI	*P* value	• Mean age 49 and female 49%, FEV_1 62%PV FRM group; mean age 46 and female 59%, FEV_1 63%PV in TEB group; mean age 48 and female 49%, FEV_1 62%PV in PLC group • Pre-study 86% of patients on ICS, 78% inh β-agonists. ICS maintained 4 weeks prior and during study • Proportion of male/female in terbutaline group differs from others • 54 patients in treatment group not included in baseline demographic analysis • Undetermined number of patients included in analysis of results • International based study (4 countries) • Pharmaceutical company funded and supported trial
				PEFR L/min				
				AM	10.9	2.3, 19.5	*P*=.014	
				PM	8.0	-4.0, 16.5	*P*=.061	
				FEV_1	0.13	0.05, 0.21	*P*<.0017	
				Symptoms:				
				Days	-0.09	-0.18,-0.01	*P*=.038	
				Nights	-0.11	-0.20,-0.02	*P*=.015	
				Rescue no. of inhalations:				
				Day-time	-0.14	-0.36,-0.08	*P*=.19	
				Night-time	-0.15	-0.31,-0.01	*P*=.074	

Table 10: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus long-acting β-agonists) in chronic asthma

Study Source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Campbell et al. 1999) RCT Grade 1+ Country: United Kingdom and Ireland	Eformoterol Turbo inh 12 µg bd V Salmeterol Accu inh 50 µg bd V Salmeterol mdi 50 µg bd Run-in 7-14 days Treatment: 8 weeks Crossover: 4 weeks	Inclusion: Age 12+ yrs $FEV_1 \geq 50\%PV$ β-agonist 10+% increase in PEFR or SA β-agonist bd on 4 of previous 7 days β-agonist 15+% in PEFR or 9+% increase than patient %PV on entry Exclusion: Use of LA β-agonist – past month	469	Results are for 8 week period AM PEFR% increase (cf. baseline) PM PEFR% increase (cf. baseline) Symptom free days % Patients with worsening asthma %	(A) Eformoterol 9.5% 6.5% 32.8 11.3	(B) SLM inh 8.7% 4.6% 34.1 11.8	(C) mdi 10.7% 8.3% 28.0 11.7	*P* value Between treatments *n.s.* *P*=.271 (AB) *P*=.344(AC) *P*=.078(BC) *n.s.* *n.s.*	• Female in study arm (A) 63%, (B) 45%, (C) 57% • Cross-over period of 4 weeks following 8 week period to assess patient device and treatment preference • Pharmaceutical sponsored trial (producers of eformeterol) • Single blind randomisation

Table 10: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus long-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Bateman et al. 1998) RCT Grade 1+ Country: Three European countries and South Africa	Combination: Salmeterol/ fluticasone Diskus inh (50/100 µg) bd and Placebo Diskus inh bd V Concurrent: Salmeterol 50 µg Diskus inh bd and fluticasone 100 µg Diskus inh bd 12 weeks	Inclusion: Age 12-78 yrs Previous 4+ weeks: Patients taking 400-500 µg daily beclomethasone or budesonide or fluticasone 200-250 µg daily Run-in period: Asthma symptom score 2+ on 3/7 run-in days AM mean PEFR 50-85% of their PEFR 15 min after 400 µg salbutamol Exclusion: Patients receiving any LA inh β-agonists and OCS previous 4 weeks Exacerbation in asthma requiring hospitalization previous 12 weeks 10+ pack years smoking	244	12 weeks	Combo SLM/FP	Concurrent SLM and FP	Difference (combo-concurrent) (90% CI)	*P* value	• Mean age 33 and female 56%, FEV_1 75%PV combination group; mean age 33 and female 59%, FEV_1 76%PV, concurrent group • International study (4 countries) • Pharmaceutical company funded and supported trial
				(change in mean PEFR L/min)					
				AM	42	33	-9 (-17,0)	*P*<.098	
				PM	36	30	-5 (-13,2)	*P*<.241	
				Drug related adverse events (%)	15%	14%		*n.s.*	

Table 10: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus long-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Wallaert et al. 1999) RCT Grade 1- Country: France	Bambuterol po 20mg nocte + placebo V Salmeterol p-mdi 50 μg bd + placebo 6 weeks	Inclusion: Age 18-70 yrs Previous 4 weeks: I/OCS 800-2000 μg daily of BUD, FLN, BDP mdi Or 400-2000 μg daily BUD inh and/or oral PDN 20 mg daily FEV_1 40-85%PV PM PEFR fall of ≥15% in run-in 3/7 nights Nocturnal awakening requiring rescue medication Exclusion: Exacerbation in asthma previous 4 weeks	117	6 weeks (change cf. run-in) AM PEFR L/min PM Mean fall in overnight PEFR% % symptom free days (mean)	BMB +28 *P*<.05 +20 *P*<.05 -8.3% *P*<.001 +23%	SLM +29 *P*<.01 +23 *P*<.001 -6.8% *P*<.001 +14%	*P* value *P*<.86 *P*<.73 N/A *P*<.55	NNT 11	• Mean age 45 and female 56%, FEV_1 64%PV (mean L) 64.1 non-smokers 66% in BMB group; mean age 46 and female 55%, FEV_1 65%PV 65, non-smokers 73% in SLM group • Treatment period efficacy variables calculated over last 4 weeks • No intention to treat analysis • 21 patients discontinued prematurely from study, treated dropped out patients not included in results, analysis accounts for n=48 in BMB group and n=57 in SLM group • Pharmaceutical company supported trial in manuscript preparation

Table 11: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus leukotriene antagonists) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Villaran et al. 1999) RCT Grade 1+ Country: 12 countries	Salmeterol inh 50 µg bd V Montelukast po 10 mg daily 8 weeks	Inclusion: Age 15-45 yrs FEV_1 improved by ≥12% post β-agonist PC_{20} 0 in FEV_1 in response to ≤ 4mg/ml methacholine or histamine ≤ 20 pack years smoking Exclusion: Asthma requiring emergency care – past month	197		MNT	SLM	*P* value		• Mean age 27 and female 50% • Exercise induced bronchoconstriction • Pharmaceutical sponsored trial (producers of montelukast) • Similar study design, authors and sponsor to next study
				Maximal % fall in FEV_1 post exercise (cf. baseline)	17.2%	10.7%	*P* < .001		
				Recovery time to within 5% of prechallenge level at 8 weeks compared with pre intervention (min)	-23.9	-11.3	*P* = .002		
								NNH	
				Adverse respiratory events (SLM cf. MNT)	39%	54%	*P* < 0.05	7	
(Edelman et al. 2000) RCT Grade 1+ Country: United States	Salmeterol inh 50 µg bd V Montelukast po 10 mg nocte 8 weeks	Inclusion: Age 15-45 yrs FEV_1 ≥ 65%PV <15 pack-years smoking Exclusion: Asthma or URTI requiring emergency care – past month	191		MNT	SLM	*P* value		• Mean age 26 and female 50% • Mod-severe activity limitation in 60% in past month at baseline • No baseline ethnicity data presented • Pharmaceutical company input (producers of montelukast) in funding, design, conduct and analysis of trial
				Maximal % challenge fall in FEV_1	57.2%	33.0%	*P* = .002		

Table 11: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus leukotriene antagonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Busse et al. 1999a) RCT Grade 1+ Country: United States	Salmeterol inh 42 µg bd V Zafirlukast po 20 mg bd 4 weeks	Inclusion: Age ≥ 12 yrs FEV_1 50-80%PV Exclusion: >10 pack years tobacco smoking	289		SLM	ZAF	*P* value	NNT	• Mean age 38 and female 80% • Mean FEV_1 66%PV • 80% on inhaled steroid pre-study • Exercise induced bronchoconstriction • Unknown proportion of participants identified through advertisements – may limit generalisability
				Improvement in am PEFR (L/min)	29.6	13.0	$P \leq 0.001$		
				Symptom free days	22.4%	8.8%	$P \leq 0.001$	7	
				% days with no rescue medication use	30.5%	11.3%	$P \leq 0.001$	5	

Short-acting beta-agonists

Chronic asthma

Table 12: Smmary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kemp et al. 1998) RCT Grade 1+ Country: United States	Salmeterol inh (breath activated device) 50 µg bd + placebo mdi Qid V Salbutamol mdi 180 mg Qid + placebo mdi bd V Placebo mdi Qid 12 weeks	Inclusion: Age 18-79 yrs FEV_1 50-80%PV $FEV_1 \geq$ +15% after 30 minutes inh of 180 µg salbutamol Exclusion: Smoker	451		SLM	SLB	*P* value	• Mean age 31 and female 39%, FEV_1 65%PV, %race non-white 3% in SLM group; mean age 31 and female 43%, FEV_1 66%PV, race non-white 12% in SLB group; mean age 31 and female 43%, FEV_1 65%PV, race non-white 9% in PLC group • Significant difference in ethnic mix across groups • Unchanged ICS or cromolyn usage previous 3 months • All patients on "as needed" salbutamol use • Two identically designed trials with pooled data results • Unclear if intention to treat methodology used and number of patients included in analysis • Pharmaceutical company funded and supported trial
				Mean Area Under Curve AUC for FEV_1 (L/hrs)				
				Day 1	5.5	4.6		
				Week 12	6.1	3.4	*P*<.001	
				(12-hour serial pulmonary function testing)				
				Mean FEV_1 %PV from				
				Day 1	81%	85%		
				Week 12	84%	82%	*P*<.001	
				Treatment related adverse events % of patients	10%	9%	N/A	
				Baseline v Weeks 1-12				
				Mean % of nights without awakening (se)	63 (2.9) 85 (1.9)	68 (2.7) 71 (2.5)	*P*<.001	
				Mean asthma symptoms score	1.2 (0.07) 0.8 (0.06)	1.0 (0.06) 0.9 (0.05)	*P*<.01	
				Mean puff/d of rescue salbutamol use	4.3 (0.2) 1.6 (0.2)	4.3 (0.2) 2.2 (0.2)	*n.s.*	

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Boulet et al. 1997) RCT Grade 1+ Country: Canada	Salmeterol inh 50 µg bd V Salbutamol mdi 200 µg Qid 12 weeks	Inclusion: Age 12-76 yrs FEV_1 50-80%PV $FEV_1 \geq 15\%$ 15 minutes after inh of 200 µg salbutamol Exclusion: Other β-agonists and OCS ICS, IMM for at least 1 month pre-study	228		SLM	SLB	*P* value	NNT	• Mean age 37 and female 44%, FEV_1 66%PV in SLM group; age 40 and female 43%, FEV_1 66%PV in SBM group • Unclear if intention to treat methodology • Inadequate data results reported for appraisal of primary FEV_1 measure of efficacy • Pharmaceutical company funded trial
				Between treatment groups: Mean improvement over baseline FEV_1 AM postdose time point					
				3-6 hours	N/A	N/A	*P*<.001		
				10-12 hours	N/A	N/A	*P*≤.012		
				(day1, weeks 4, 8, 10, 12)					
				Mean post-dose changes in FEV_1 %	8.1%	9.7%	N/A		
				Mean improvement in AM PEFR(l/min)	35	-3	*P*<.001		
				% days no symptoms	29%	15%	*P*=.012	7	
				% nights no awakenings	14%	-1%	*P*<.001	7	

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Martin et al. 1999) CO Grade 1+ Country: United States	Salbutamol po (extended release) 4mg AM, 8 mg PM bd V Salmeterol inh 42 µg bd Treatment period(s) 3 weeks each 7-9 day washout	Inclusion: Age 18-65 yrs FEV_1 50-80%PV FEV_1 > 12% after inh salbutamol Stable asthma for previous 30 days Exclusion: Systemic CS β-agonists other than rescue salbutamol Theophylline (sustained release)	47		SLM	SLB	*P* value	NNT	• Mean age 35 and female 48%, FEV_1 67%PV, 61% of patients on ICS pre-study, 27% tobacco use history. • No baseline demographics for randomized treatment groups • Nocturnal asthma defined as ≥ 15% decrease in AM and night FEV_1 on 3/7 nights prior to randomization • 46/47 patients included in analysis, 1 lost to follow-up • Pharmaceutical company funded and supported trial
				Adjusted means					
				FEV_1 (l)	2.70	2.71	*n.s.*.		
				PEFR L/min AM	420	414	n.s.		
				% overnight change PEF	-7.9	-7.2	*n.s.*.		
				% overnight change FEV_1	-5.1	-4.0	*n.s.*.		
				Rescue salbutamol (no. of inhalations/day)	2.20	2.98	*P*=.001		
				% of no nighttime awakenings	84.6%	79.4%	*P*=.021	22	

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Ekstrom et al. 1998b) RCT Grade 1+ Country: 3 Scandinavian countries	Formoterol inh 12 µg (delivered dose 9 µg) bd + placebo V Terbutaline inh 0.5 mg Qid V Placebo inh Qid 12 weeks	Inclusion: Age 18-82 yrs FEV_1 50-80%PV $FEV_1 \geq 15\%$ 15 minutes after inh of 0.5 mg turbutaline	343		FRM vs placebo	FRM vs TEB	TEB vs Placebo	• Mean age 49 and female 49%, FEV_1 62%PV , current/past smoker 62% in SLM group; mean age 48 and female 59%, FEV_1 61%PV, current/ex smoker 57% in TEB group; mean age 47 and female 49%, FEV_1 60%PV, current/ex-smoker 63% in PLC group • 89% of patients on ICS pre-study. Patients allowed to use ICS and terbutaline as rescue medication • International based study (3 countries) • Unclear if intention to treat methodology • Pharmaceutical company funded and supported trial
				Mean difference in improvement over baseline				
				PEFR L/min AM	14.6	21.9	-7.2	
				PM	16.2	16.7	-0.6	
				Asthma symptoms – night	-0.20	-0.16	-.0.05	
				Rescue medication (no. of inhalations)				
				Day	-0.53	-0.10	-0.43	
				Night	-0.67	-0.11	-0.56	
				P value				
				PEFR L/min AM	*P*=.0022	*P*=.0001	*n.s.*.	
				PM	*P*=.0001	*P*=.0001	n.s.	
				Asthma symptoms – night	*P*=.0025	*P*=.019	n.s	
				Rescue medication (no. of inhalations)				
				Day	*P*=.013	*n.s.*.	*P*=.043	
				Night	*P*=.0042	n.s.	*P*=.015	

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Lipworth et al. 1998) RCT Grade 1+ Country: Scotland	Formoterol inh 6 µg (delivered dose 4.5 µg) bd + placebo V Formoterol inh 24 µg (delivered dose 9 µg -2 puffs) bd + placebo V Formoterol inh 12 µg daily (delivered dose 9 µg) + placebo V Terbutaline inh 500 mg Qid V Placebo inh Qid Methacholine challenge (MCh) 3.125 µg - 6400 µg to FEV_1 PD_{20} 2 weeks	Inclusion: Age 16-65 yrs $FEV_1 \geq 60\%PV$ PD_{20} (MCh) ≤1000 µg Constant dosage of ICS ≤2000 µg BUD, BDP or FP Exclusion: Patients on OCS previous 4 weeks Smoker previous 12 months	72	Methacholine protection ratios compared with placebo	Geometric Mean fold Protection Ratio	95% CI	*P* value	• Mean age 33 and female 47%, FEV_1 90%PV FRM 24 µg group; mean age 36 and female 53%, FEV_1 87%PV in FRM 12 µg group; mean age 39 and female 71%, FEV_1 85%PV in FRM 6 µg group; mean age 42 and female 50%, FEV_1 88%PV in TEB 500 µg group; mean age 38 and female 43%, FEV_1 86%PV in placebo group • Unclear if intention to treat methodology • Pharmaceutical company funded and supported trial
				Formoterol 24 µg bd				
				First dose	10.2	4.6 – 22.5	N/A	
				14 days	1.4	0.6 – 3.4	N/A	
				Formoterol 12 µg bd				
				First dose	6.4	2.9 – 14.1	N/A	
				14 days	1.5	0.6 – 3.8	N/A	
				Formoterol 6 µg bd				
				First dose	5.5	2.5 – 12.3	N/A	
				14 days	1.6	0.6 – 4.0	N/A	
				Terbutaline 500 µg Qid				
				First dose	3.4	1.5 – 7.8	N/A	
				14 days	1.9	0.8 – 4.9	N/A	
				Pre-challenge FEV_1 1 hour after use of medication After 14 days of treatment (as % ratio versus placebo)				
				Formoterol 24 µg bd	109%	103,116%	*n.s.*	
				Formoterol 12 µg bd	111%	105, 118%	*n.s.*	
				Formoterol 6 µg bd	109%	102, 115%	*n.s.*	
				Terbutaline 500 µg Qid	105%	99, 112%	*n.s.*	

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Seberova and Andersson 2000) CO Grade 1- Country: Czech Republic	5 study visits, with single doses: minimum 2 days washout Formoterol inh 4.5 µg or 9 µg V Salbutamol mdi 100 µg or 200 µg V Placebo	Inclusion: Age 18-64 yrs $FEV_1 \geq 40\%PV$ $FEV_1 \geq 1.51$ $FEV_1 \geq 15\%$ 15 minutes after inh of 0.5 mg terbutaline Exclusion: If FEV_1 not within ±12% of baseline FEV_1 patients asked to return another day Oral, inh long-acting β-agonists, GCS during study	36	FEV_1 at 3 minutes after inhalation	% Increase in FEV_1 (cf. baseline	*P* value cf. placebo		• Mean age 34 and % female unknown, mean FEV_1 (L) 2.75 • No baseline demographics for randomized treatment groups • Treatment period undefined • Randomized at each study visit • No power analysis for study sample size • Pharmaceutical company funded and supported trial
				Salbutamol 100 µg	+10.0%	*P*<.001	Between groups	
				Salbutamol 200 µg	+11.4%	*P*<.001		
				Formoterol 4.5 µg	+11.7%	*P*<.001		
				Formoterol 9.0 µg	+11.8%	*P*<.001	*n.s.*	

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Lipworth et al. 1999) RCT Grade 1- Country: Scotland	Formoterol inh 12 µg mane V Formoterol inh 6 µg bd V Formoterol inh 24 µg bd V Terbutaline inh 500 µg Qid 2 weeks	Inclusion: Age 18-45 yrs $FEV_1 \geq 60\%PV$ PD_{20} in FEV_1 response to methacholine challenge of 1000 µg and 2-doubling dose protection in response to a single test dose of formoterol inh 24 µg Non-smoker	38	Mean values	FRM 6 µg bd	FRM 12 µg daily	FRM 24 µg bd*	TEB 500 µg Qid	• N=8, mean age 39 and female 38%, FEV_1 80%PV in FRM 6 µg group; N=10, age 41 and female 40%, FEV_1 84%PV in FRM 12 µg group; N=11, age 32 and female 45%, FEV_1 91%PV in FRM 24 µg group; N=11, age 36 and female 44%, FEV_1 87%PV in TEB group • Small numbers in each treatment group, no significant demographic differences between groups • All patients on regular ICS therapy. On demand β-agonists • Unclear if intention to treat methodology • Results presented are only secondary outcome measures. Primary outcome bronchoprotective sensitivity • Pharmaceutical support in provision of inhalers for trial
				AM PEFR(L/min)(se) run-in	395 (55)	367 (44)	447 (30)	429 (46)	
				Treatment	415 (59)	391 (21)	490 (24)	428 (45)	
				PM PEFR(L/min)(se) run-in	398 (50)	417 (31)	471 (27)	435 (51)	
				Treatment	433 (59)	421 (25)	502 (24)	445 (46)	
				* *P*<.05 difference between run-in and treatment only in formoterol 24 µg bd group					

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Tattersfield 2001) RCT Grade 1+ Country: 4 European countries	As needed basis: Formoterol inh 4.5-54 µg daily V Terbutaline inh 0.5-6 µg daily 12 weeks	Inclusion: Age 18-75 yrs $FEV_1 \geq 50\%PV$ ICS mean dose 870 µg daily previous 4 weeks Requirement of β-agonists average 3/8 times during run-in period Exclusion: Patients inh 12+ rescue medication	362	Number at risk (remaining w/o severe asthma exacerbation) Days since randomization 0 20 40 60 80 Exacerbations: no. of patients/no. of exacerbations Need for OCS Mean difference in change over treatment (FRM-TEB) AM PEFR(L/min)(95% CI) PM PEFR(L/min)(95% CI) Diurnal variation % Symptom score – Day Night	FRM 182 173 165 153 146 26 / 29 21/26 (81%) 11 (3,20) 8 (0,15) -0.4 (-1.4,0.6) -0.04 -0.02	TEB 180 159 144 132 127 43 / 48 31/43 (72%)	*P* value *P*=.013 *P*=.009 *P*=.043 *P*=.44 *P*=.54 *P*=.68	• Mean age 46 and female 52%, FEV_1 74%PV in FRM group; mean age 48 and female 62%, FEV_1 74%PV in TEB group • Severe exacerbations defined by need for OCS or fall in PEFR of 30% from baseline on 2 consecutive days • International study (4 countries) • Pharmaceutical company funded and supported trial

Table 12: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus short-acting β-agonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Ekstrom et al. 1998a) RCT Grade 1- Country: 4 European countries	Formoterol inh 6 µg (delivered dose 4.5 µg) bd V Terbutaline inh 0.5 mg Qid V Placebo inh Qid 12 weeks	Inclusion: Age 18-79 yrs FEV_1 40-80%PV $FEV_1 \geq$ +15% and 200+ ml after inh of 0.5 mg terbutaline	397		FRM vs TEB	95%CI	*P* value	• Mean age 49 and female 49%, FEV_1 62%PV FRM group; mean age 46 and female 59%, FEV_1 63%PV in TEB group; mean age 48 and female 49%, FEV_1 62%PV in PLC group • Pre-study 86% of patients on ICS, 78% inh β-agonists. ICS maintained 4 weeks prior and during study • Proportion of male/female in terbutaline group differs from others • 54 patients in treatment group not included in baseline demographic analysis • Undetermined number of patients included in analysis of results • International based study (4 countries) • Pharmaceutical company funded and supported trial
				PEFR L/min				
				AM	10.9	2.3, 19.5	*P*=.014	
				PM	8.0	-4.0, 16.5	*P*=.061	
				FEV_1	0.13	0.05, 0.21	*P*<.0017	
				Symptoms:				
				Days	-0.09	-0.18,-0.01	*P*=.038	
				Nights	-0.11	-0.20,-0.02	*P*=.015	
				Rescue no. of inhalations:				
				Day-time	-0.14	-0.36,-0.08	*P*=.19	
				Night-time	-0.15	-0.31,-0.01	*P*=.074	

Table 13: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus short-acting beta-agonist) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Hancox et al. 1999b) CO Grade 1+ Country: New Zealand	Budesonide inh 400 µg bd + terbutaline inh 1000 µg Qid V Budesonide inh 400 µg bd V Terbutaline inh 1000 µg Qid V Placebo 6 weeks each	Inclusion: Age 9-64 yrs Exclusion: Current or ex cigarette smoker (>5 pack years) Pharmaceutical limitations	61		BDP/TEB	BDP	TEB	• Mean age 27 and female 69% • Participants able to tolerate the withdrawal of inh steroid • Pharmaceutical company involved in supplying inhalers and supporting the lead author • No baseline comparison post-randomisation
				Δ AM PEFR (cf. BDP)	14			
				(95%CI)	(5,23)			
				Δ am PEFR (cf. TER)	27			
				(95%CI)	(17,37)			
				Night awakening (%)	1.9	3.4	4.0	
				P value	*n.s.*	*n.s.*	*n.s.*	
				Rescue medication use (puffs/day)	0.3	0.5	0.5	
				P value	*n.s.*	*n.s.*	*n.s.*	
(Aldridge et al. 2000) CO Grade 1+ Country: New Zealand	Budesonide inh 400 µg bd + terbutaline inh 1000 µg Qid V Budesonide inh 400 µg bd V Terbutaline inh 1000 µg Qid V Placebo 6 weeks each	Inclusion: Age 16-64 yrs FEV_1 > 50%PV Exclusion: Current or ex-cigarette smoker (>5 pack years) Pharmaceutical limitations	34		BDP/TEB	BDP	TEB	• Mean age 39 and female 47% • Mean FEV_1 90%PV • No baseline comparison post-randomisation • 82% of participants randomised were analysed • Pharmaceutical company involved in supplying inhalers and supporting the lead author • Selected from participants in (Hancox et al. 1999b)
				AM PEFR (L/min)	491 *P* =.0011 *P* < .0012	469 *P* = 0.043	450	
				Daytime wheeze (% days present)	4 *n.s.*[1] *P* = .02[2]	9 *n.s.*[3]	18	
				Nighttime wheeze (% days present)	3 *n.s.*[1] *P* = .003[2]	4 *n.s.*[3]	12	
				Rescue med use (Median % days used)	0 *P* =.05[1] *n.s.*[2]	0 *n.s.*[3]	0	
				[1]Combined versus BDP, [2]combined versus TEB, [3]BDP versus TEB				

Table 13: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus short-acting beta-agonist) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Hancox et al. 1999a) CO Grade 1- Country: New Zealand	Budesonide inh 400 µg bd + terbutaline inh 1000 µg Qid V Budesonide inh 400 µg bd V Terbutaline inh 1000 µg Qid V Placebo 6 weeks each	Inclusion: Age 16-64 yrs Exclusion: Current or ex-cigarette smoker (>5 pack years) Pharmaceutical limitations	34	% fall FEV_1 post methacholine (95%CI)	BDP/TEB 25.9 (22.2, 28.2)	BDP 26.1 (22.3, 28.3)	TEB 26.9 (24.4, 28.5)	• Female 47% • Mean FEV_1 90%PV • No baseline comparison post-randomisation • 76% of participants randomised were analysed • Pharmaceutical company involved in supplying inhalers and supporting the lead author • Selected from participants in (Hancox et al. 1999b)

Table 14: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists regular versus PRN treatment) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Richter et al. 2000) CO Grade 1+ Country: Germany	Salbutamol/ Fenoterol Qid and PRN V Salbutamol/ Fenoterol PRN 24 weeks each	Inclusion: Age 18-75 yrs All patients on regular β-agonist and inhaled steroid for at least 2 years	80		PRN	Reg	*P* value	• Mean age 48 and female 74% • Mean FEV_1 74%PV • Single blind • Analysed 91% of participants randomised • No data on baseline comparison post-randomisation
				Asthma attack (n/day)	0.58	0.45	*n.s.*	
				Night awakening (n/night)	0.15	0.09	*n.s.*	
				Symptom score	1.46	1.40	*n.s.*	
				Rescue med use (puffs/night)	0.34	0.26	*n.s.*	
				Absence from work/school (n)	16	9	*n.s.*	
				ED treatment (n)	12	5	*n.s.*	
				FEV_1 %PV	85.2	81.2	*P*= 0.003	

Acute asthma

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Rodrigo and Rodrigo 2000) RCT Grade 1+ Country: Uruguay	Salbutamol mdi 120 µg/puff + Ipratropium mdi 21 µg/puff in a dose of 4 puffs at 10 min intervals (480 µg/84 µg) V Salbutamol mdi 120 µg/puff in a dose of 4 puffs at 10 min intervals (480 µg) 3 hours of treatment (24 puffs or 2,880 µg salbutamol and 504 µg ipratropium per hour)	Inclusion: Age 18-50 yrs FEV_1/PEFR < 50% PV	180		SLB+IPR	SLB	*P* value	NNT	• Mean age 35 and female 37%, PEFR 32%PV in SLB+IPR group; mean age 33 and female 34%, PEFR 33%PV in SLB group • Acute asthma, Emergency Department setting
				Improvement over salbutamol control group %					
				PEFR (95%CI)	+20% (2.6,38.4)		*P*=.02		
				FEV_1 (95%CI)	+48% (19.8,76.4)		*P*=.001		
				Hospital admissions n (%)	18 (20%)	36 (39%)	*P*=.01	5	
				Pre ED use of β-agonists by ipr patients: increase in FEV_1					
				previous use	N/A	N/A	*P*=.01		
				no previous use	N/A	N/A	*P*=.03		
				Symptoms					
				24+ hours	N/A	N/A	*P*=.01		
				< 24 hours	N/A	N/A	*P*=.09		
				$FEV_1 \leq$ 30PV%	N/A	N/A	*P*=.001		
				> 30PV%	N/A	N/A	*P*=.60		

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Weber et al. 1999) RCT Grade 1+ Country: United States	All patients received prednisone po 60 mg Salbutamol neb 10 µg/hour + Ipratropium neb 1.0 µg/hour V Salbutamol neb 10 µg/hour + Ipratropium neb 1.0 µg/hour ≤ 3 hours of treatment	Inclusion: Age 18+ yrs FEV_1/PEFR < 70% PV after 2.5 mg Salbutamol in 3 mL normal saline	67		SLB+IPR	SLB	*P* value	• Mean age 46 and female 75%, PEFR 50%PV and smoking history 48% in SLB+IPR group; mean age 49 and female 66%, PEFR 40%PV and smoking history 74% in SLB group • Significant *P*<.05 baseline differences in PEFR%PV and smoking history. *P*<.10 differences in previous hospitalization and intubation • Results have been adjusted for baseline differences • Acute asthma, Emergency Department setting • Pharmaceutical (producer of ipratropium) involvement in supply of ipratropium and pharmacy costs
				Improvement over salbutamol control group % PEFR (95%CI)				
				Adjusted for baseline PEFR	+6.3% (-1.5,27%)		*n.s.*	
				Median length of stay (minutes)	210	245	*P*=.03	
				Adjusted for baseline PEF	N/A	N/A	*P*=.26	
				Hospital admissions n (%)	8 (23%)	13 (39%)	N/A	
				Adjusting for baseline PEF OR (95%CI)	0.88 (0.28, 2.8)			

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Lin et al. 1998) RCT Grade 1+ Country: United States	Salbutamol 2.5 mg + Ipratropium 0.5 mg (first dose only) then every 20 min 2 more doses of salbutamol only (total 3 doses) neb V Salbutamol 2.5 mg + placebo (first dose only) then every 20 min 2 more doses of salbutamol only (total 3 doses) neb Treatment period 1 hour	Inclusion: Age 18+ yrs PEFR <200 L/min Exclusion: 20 pack years+ smoker β-agonists preceding 4 hours	55		SLB+IPR	SLB	*P* value	NNT	• Mean age 40 and female 54% in SLB + IPR group, mean age 41and female 59% in SLB group • Acute asthma. Convenience sample selected from Emergency Department
				Number of patients admitted to hospital n (%)	3 (11%)	10 (36%)			
				Difference and 95%CI of proportion admitted	25% (3%,46%)		*P*=.03	4[1]	
				PEFR L/min mean			Over 1 hour		
				BL	131	142	period		
				20 min	197	197			
				40 min	252	218			
				60 min	269	228	*P*=.001		
				PEFR L/min %PV mean					
				BL	28	29	Over 1		
				20 min	42	37	hour		
				40 min	53	45	period		
				60 min	57	47			
							P<.001		

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Rodrigo et al. 1999) MA Grade 1+	Ipratropium inh 0.5 µg (single dose) plus β-agonists (Salbutamol 8 studies, fenoterol 2 studies) after arrival in ED V β-agonists alone First 90 minutes of treatment	Inclusion: Age 16+ yrs English language studies RCT, double blind Patients with acute asthma, treated in ED with β-agonists Search: 1978-1999 (April) MEDLINE, Science Citation Index, Current Contents, reviews (articles and primary research), experts	1483		β-agonist + IPR	*P* value	NNT	• 10 studies included, acute asthma, mean age 32 ± 13 years and female 64% • Mean methodology quality score 0.66 (max = 1) • Criteria for discharge and admission not clearly defined • Reported adverse effects not assessed nor delivery devices
				Overall effect size (std units) cf. control group				
				FEV_1 (95%CI)	0.14 (0.04,0.24) (10%) (2%, 18%)	*P*=.008		
				Homogeneity test		*P*>.5		
				Study specific effects	(0.03-0.63)	N/A		
				Mean FEV_1 at admission <35%PV (4 studies) (95%CI)	0.38 (0.09,0.67)	N/A		
				Use of corticosteroids (7 studies) (95%CI)	0.14 (0.00,0.28)	N/A		
				Hospital admissions (5 studies) (Odds Ratio, 95%CI)	0.62 (0.44,0.88)	*P*=.007	18	

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes		Comments
(Stoodley et al. 1999) MA Grade 1+ Country: Canada	Ipratropium plus β-agonists mdi or neb after arrival in ED V β-agonists alone 30-90 minutes duration of treatment	Inclusion: Age 18+ yrs RCT (double blinding not necessary but all included studies double blind) Patients with acute asthma, treated in ED or similar with β-agonists Search: MEDLINE (1966-97), EMBASE (1980-97), CINAHL (1982-97), Biological Abstracts (1990-97), Cochrane database and Current Contents (1996-97)	1377		β-agonist + IPR	• 10 studies included, acute asthma, mean age range for treatment group 29.5-50.4 years, control group 29.6-53.2. • Study quality assessment limited to randomization, double blinding and inclusion of data for dropouts and withdrawals • Dosages of ipratropium not specified • Changes in airflow assessment FEV_1 (4 studies) PEFR (5 studies) both (1 study) • Significant Cochran Q test for homogeneity (p=.047) suggesting included trials were a heterogeneous group. One trial had much lower baseline PEFR values. Removal resulted in Q test P= .37, summary effect value 0.35 (.24,.47). Study results reported including 10 studies.
				Overall effect size (std units) cf. control group PEFR/ FEV_1 (95%CI)	0.38 (0.27,0.48)	
				% improvement in FEV_1 (4 studies)	7.3% (3.8%, 10.9%)	
				% improvement PEFR (5 studies)	22.1% (11.0%, 33.2%)	
				Hospital admissions (3 studies, n=1064) (Relative Risk, 95%CI)	.73 (53, .99)	
				Effect size of studies with IV steroids (4 studies) to all enrolled patients	.25 (.10,.40)	

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Garrett et al. 1997) RCT Grade 1- Country: New Zealand	All patients received IV hydrocortisone 200 mg within 15 minutes of treatment start (Combivent)™ Ipratropium neb 1.5 mg in a dose + Salbutamol neb 2.5 mg V Salbutamol neb 2.5 mg Duration 90 minutes	Inclusion: Age 18-55 yrs FEV_1< 70% PV Exclusion: Smoking history of 10+ pack years Complicating illness eg COPD	338		SLB + IPR	SLB	*P* value	NNT	• Mean age 30 and % female not specified, FEV_1 40%PV in SLB+IPR group; mean age 30, % female not specified, FEV_1 40%PV in SLB group • Overall % female 61%, 17% Maori, 24% Pacific Island ethnicity • 13% of patients reported using OCS, 32% ICS, 80% inh β-agonist within 6 hours of presentation to ED • Acute asthma, Emergency Department setting • No intention to treat based analysis, 58 patients (27 in combivent™ group and 31 in salbutamol group) withdrawn after treatment received (no FEV_1 recorded). • Pharmaceutical company supported study
				Mean absolute difference over salbutamol group					
					40 (57)				
				Baseline FEV_1ml (se)	93 (24)		*P*=.4485		
				45 minutes	113 (18)		*P*=.03		
				90 minutes (primary efficacy)			*P*=.02		
				FEV_1< 1 L at baseline:					
				Δ FEV_1 (mls)	22		*n.s.*		
				FEV_1≥ 1 L/min at baseline:					
				Δ FEV_1 (mls)	176		*P*<.005		
				Hospital admissions (%)	15.3%	22.3%		14	

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(FitzGerald et al. 1997) RCT Grade 1- Country: Canada	All patients received oxygen and IV bolus of 125 mg methyl-prednisone (within 15 minutes of nebulization) (Combination) Ipratropium neb 0.5 mg in a dose + salbutamol neb 3.0 mg V Salbutamol neb 3.0 mg Duration 90 minutes	Inclusion: Age 18-55 yrs FEV_1< 70% PV Exclusion: Smoking history of 10+ pack years COPD or significant other medical illness	342		SLB+IPR	SLB	*P* value	NNT	• Mean age 31 and female 60%, FEV_1 1.62L in SLB+IPR group; mean age 30, % female 64%, FEV_1 1.53L in SLB group • Prior asthma medication in combination and salbutamol alone groups: 12% and 12% of patients reported using OCS, 46% and 40% ICS, 88% and 90% inh β-agonist within 24 hours of presentation to ED • Acute asthma, Emergency Department setting • Poor description of randomisation, concealment and blinding methodology • Not strict intention to treat based analysis • Criteria for discharge and admission not clearly defined • Pharmaceutical company partly funded study
				Mean change from baseline					
				Baseline FEV_1 L (se)	1.62 (0.05)	1.53 (0.05)	*n.s.*		
				45 minutes	0.58 (0.04)	0.52 (0.04)	*n.s.*		
				90 minutes (primary efficacy)	0.61 (0.04)	0.52 (0.04)	*n.s.*		
				Hospital admissions (%)	5.9%	11.2%		19	

Table 15: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists + ipratropium versus short-acting β-agonists) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kamei et al. 1999) RCT Grade 1- Country: Japan	Fenoterol 1 puff (200 µg/puff) every 1 minute for 5 minutes, total 1000 µg + Oxitropium bromide 2 puffs (100 µg/puff) every 1 minute for 5 minutes, total 1000 µg mdi with InspirEase™ holding chamber V Fenoterol 1 puff (200 µg/puff) every 1 minute for 5 minutes, total 1000 µg Treatment duration 60 minutes	Inclusion: FEV_1 < 70% PV Exclusion: Pulmonary emphysema Complicating drugs	69	At 60 minutes Mean value cf. baseline PEFR L/min (se) From baseline PEFR % impr 1 min 15 min 30 min 60 min	FRM + OTB 261 (18) N/A N/A N/A N/A	FRM 210 (17) N/A N/A N/A N/A	*P* value *P*<0.05 *P*<0.02 *P*<0.01 *P*<0.02 *P*<0.001	• Mean age 55 and female 46%, best FEV_1 1.81L in FRM+OTB group; mean age 56and female 65%, best FEV_1 1.86L in FRM group • Acute asthma, Emergency Department setting • Open study, no detail on randomisation nor statistical power • Intention to treat based analysis not evident, 31/34 and 33/35 in respective randomised groups analyzed for efficacy • Some data results for primary efficacy outcome not reported

Table 16: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists dose or administration methods) in acute asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Nouira et al. 1999) RCT Grade 1+ Country: Tunisia	Salbutamol neb 10 mg V 5 mg 30 minutes	Inclusion: Age > 16 years PEFR < 50%PV and ≥ 2 of: pulse>100, Resp rate > 30, accessory muscle use, pulsus paradoxus > 20. Exclusion: Incapable of performing PEFR Intubated Age > 65 years and history of severe cardiopulmonary disease	40	% Δ PEFR	5 mg 12	10 mg 11	*P* value *n.s.*		• Mean age 41 and female 40% • Mean PEFR 29%PV • All patients received hydrocortisone 100 mg IV • 90% power to detect a 20% difference in PEFR at the 5% significance level
(Emerman et al. 1999) RCT Grade 1+ Country: United States	Salbutamol neb 2.5 mg (3 doses) V Salbutamol neb 7.5 mg (3 doses)	Inclusion: Age 18-50 yrs Presenting to ED for acute asthma Able to perform spirometry	160	FEV_1 %PV Admitted (%) Relapse within 7 days (%) Side effects attributable to salbutamol (%)	Low dose 50.6 43 17.1 49.4	High dose 56.3 39 16.7 44.2	*P* value *P* = 0.06 *P* = 0.65 *P* = 0.70 *P* = 0.51		• Mean age 37 and female 77% • Mean FEV_1 40%PV • 80% power to detect 17% difference in increase in FEV_1 from baseline at 5% significance level • Unclear whether ITT analysis was used
(Karpel et al. 1997) RCT Grade 1+ Country: United States	Salbutamol mdi + Spacer 540 µg at time: 0, 30, 60, 90 mins V 0, 60 mins V 0 mins 2 hours	Inclusion: Age 18-55 years FEV_1 ≤ 60%PV Cigarette smoking ≤ 10 pack-years Able to perform pulmonary function tests	100	FEV_1 (L) Additional β-agonist use (%) Received systemic steroid (%) Hospitalised (%)	4 dose 2.2 20.6 32.4 3.0	2 dose 2.2 23.5 20.6 5.9	1 dose 1.7 42.4 21.2 3.0	*P* value *P* <.05 (4 V 1 dose, 2 V 1 dose) *P* <.05 (4 V 1 dose, 2 V 1 dose) *n.s.* *n.s.*	• Mean age 32 and female 73% • Mean FEV_1 42%PV • Financial support from pharmaceutical company • Randomisation process not described

Table 16: Summary of studies investigating the effect of pharmaceuticals (short-acting β-agonists dose or administration methods) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Besbes-Ouanes et al. 2000) RCT Grade 1+ Country: Tunisia	Salbutamol neb 27.5 mg over 6 hours: Continuous V Intermittent 6 hours	Inclusion: PEFR < 50%PV and 2 of pulse ≥ 120, resp rate ≥ 30, pulsus paradoxus ≥ 15 mm Hg, accessory muscle use, SaO2 < 92% (room air), PaCO2 > 42 mm Hg	42		INT	CON	*P* value	• Mean age 40 and female 60% • Mean PEFR 24%PV • All patients received IV hydrocortisone • Some doubts about the success of double blinding • 80% power to detect a 13% difference in PEFR at the 5% significance level
				Δ PEFR (%)	32	30	*n.s.*	
				Δ clinical severity score	-6.1	-6.3	*n.s.*	
				Required supplemental treatment (%)	9.5	14	*n.s.*	
(Bradding et al. 1999) RCT Grade 1- Country: United Kingdom	Salbutamol neb 5 mg q4h V Salbutamol 2.5-5 mg PRN 24 hrs post-hosp admission to 24 hrs prior to discharge	Inclusion: Age 17-65 yrs Presenting to ED for acute asthma	46		PRN	q4h	*P* value	• Mean age 30 and female 70% • Open study • Inadequate randomisation method
				Length of stay (days)	3.7	4.7	*P* = 0.04	
				Number of nebs	7.0	14.0	*P* = .003	
				Patients with tremor	4	11	*P* = 0.06	
				Patients with palpitations	1	7	*P* = 0.05	
(Hoffman and Smithline 1997) RCT Grade 1- Country: United States	Circulaire™ nebuliser V Conventional nebuliser (Airlife Misty-Neb™) Single dose	Inclusion: Presenting to ED requiring β-agonist nebuliser Exclusion: Incapable of performing PEFR	134		CIR	CNV	*P* value	• Mean age 45 and female 45% • Single blind • Baseline difference in diastolic BP • Circulaire nebuliser provided by pharmaceutical company
				Median PEFR (L/min)	80	30	*P* < .001	

Steroids

Chronic asthma

Table 17: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus theophylline) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Reed et al. 1998) RCT Grade 1+ Country: United States	Beclomethasone inh 84 µg Qid V Theophylline 1 year	Inclusion: Age 6-65 yrs FEV_1 >50%PV Exclusion: >5 pack years tobacco smoking Resp infection in past 3 weeks Pharmaceutical limitations	747		BEC	THP	*P* value	NNT	• Female 51% • 45% previously taken theophylline, 4% beclomethasone • 75% study completion rate • Theophylline dose determined by response • Study supported by phamaceutical company producing beclomethasone • No baseline data on mean age in two study groups • [1]For any day in the 12th month. There were significant differences in earlier months that favoured beclomethasone.
				Moderately severe or worse symptoms[1]	25.8%	30.5%	*n.s.*		
				Systemic steroid use over course of study	20%	29%	*P* = .009	11	
(Ukena et al. 1997) RCT Grade 1+ Country: Germany, Hungary, Austria	Beclomethasone inh 200 µg bd + Theophylline V Beclomethasone inh 400 µg bd 6 weeks	Inclusion: Age 18-70 years FEV_1 50-85%PV Asthma not controlled on beclomethasone 400 µg daily or equivalent Exclusion: Severe asthma attack or lower resp infection within 1 month Current smoker Pharmaceutical limitations	133		Combined	BEC	*P* value		• Median age 48 and female 44% • FEV_1 75%PV • Data not presented but no significant difference in rescue med use between groups • ITT analysis not presented in paper but results similar to per protocol analysis presented • Producers of theophylline funded and supported trial
				Δ FEV_1 (L)	0.26	0.19	*n.s.*		

Table 17: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus theophylline) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Evans et al. 1997) RCT Grade 1+ Country: United Kingdom and Sweden	Budesonide inh 400 µg bd + theophylline po 250 mg (if < 80 kg) or 375 mg (if ≥ 80 kg) bd V Budesonide inh 800 µg bd 3 months	Inclusion: FEV_1 > 50%PV Exclusion: Pharmaceutical limitations Asthma exacerbation within 3 weeks of run in	62		THP + BDP	BDP	*P* value	• Mean age 39 and female 60% • Mean FEV_1 75%PV • Supported by pharmaceutical company that produces theophylline
				Improvement in FEV_1 (L)	0.21	0.11	*P* = 0.03	
				Improvement in FVC (L)	0.26	0.18	*P* = 0.03	
				Day time symptom scores	N/A	N/A	*P* = 0.26	
				Night time symptom scores	N/A	N/A	*P* = 0.59	
				Daytime rescue med use	N/A	N/A	*P* = 0.57	
				Nighttime rescue med use	N/A	N/A	*P* = 0.97	

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma

Study source, design and evidence grading	Intervention Comparison And study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Shrewsbury et al. 2000) MA Grade 1+	Salmeterol + inhaled steroids (Beclo-methasone 5 studies or fluticasone 4 studies) V At least doubling dose of inhaled steroids (Beclo-methasone 5 studies or fluticasone 4 studies) 12+ weeks	Inclusion: Age 12+ yrs RCT, double blind All languages Patients with symptomatic asthma, treated on current dose of inhaled steroids Search: 1985-1999 (September 1999 last search) MEDLINE, EMBASE, GlaxoWellcome databases	3685	Treatment with salmeterol plus inhaled steroids versus increased dose inhaled steroids (double+ dose) Mean difference (95% CI) in lung function	3 months	6 months	*P* value 3 months	*P* value 6 months	• 9 studies included • No evidence of heterogeneity between studies for PEFR and FEV_1 and exacerbation analysis. For symptoms and rescue comparison *P*<.10 in all cases. Comparison of 95% CI under fixed and random effects model cited by authors as small and clinically unimportant (data not provided) • Pharmaceutical company supported meta-analysis
				AM PEFR L/min	22.4 (15,30)	27.7 (19,38)	*P*<.001	*P*<.001	
				AM FEV_1 L	0.10 (0.04, 0.16)	0.08 (0.02,0.14)	*P*<.001	*P*<.01	
				Mean % difference (95% CI)					
				Days without symptoms	11% (8,15)	15%(11,19)	*P*<.001	*P*<.001	
				Nights without symptoms	5% (2,8)	6% (3,9)	*P*<.001	*P*<.001	
				Days without rescue treatment	16% (13,20)	19% (14,24)	*P*<.001	*P*<.001	
				Nights without rescue treatment	9% (5,12)	9% (5,13)	*P*<.001	*P*<.001	
				Difference (95% CI) in mean numbers of patients with exacerbation:					
				Any exacerbation	2.73 (0.43,5.04)		*P*=.02		
				Moderate/severe exacerbation	2.42 (0.24,4.60)		*P*=.03		

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Baraniuk et al. 1999) RCT Grade 1+ Country: United States	Fluticasone mdi 220 µg bd V Triamcinolone mdi 600 µg bd V Fluticasone mdi 88 µg bd + salmeterol mdi 42 µg bd 12 weeks	Inclusion: Age 12+ yrs FEV_1 40-65%PV Patients with FEV_1 65-85%PV 15+% increase in FEV_1 %PV after 30 min with 180 µg salbutamol BDP dosage 252-672 µg, or TAA 600-1000 µg, or FP 1000 µg daily 3+ months pre-study Exclusion: Smoker Serious asthma exacerbation previous 4 weeks	680	12 weeks (mean change cf. baseline) (se) AM FEV_1 (L) FEV_1 (L) %PV Symptom score % symptom-free days % rescue-free days Adverse event related to treatment (% patients) (mean change cf. baseline) (se) AM FEV_1 (L) FEV_1 (L) %PV Symptom score % symptom-free days % rescue-free days Adverse event related to treatment (% patients)	FP plus SLM 0.58 (0.03) 16.7 (1.0) -0.44(0.05) 29.2(2.9) 45.0(2.9) 14% FP 0.48(0.03) 14.0(0.6) -0.46(0.05) 22.6(2.6) 28.9(2.7) 13%	TAA 0.34 (0.03) 10.4 (0.80 -0.31(0.05) 11.9(2.1) 27.4(2,5) 8% TAA 0.34(0.03) 10.4(0.80 -0.31(0.05) 11.9(2.1) 27.4(2,5) 8%	*P* value *P*<.001 *P*≤.004 *P*≤.004 *P*≤.004 *P*≤.004 N/A *P* value *P*≤.027 *P*≤.035 *P*≤.035 *P*<.001 *n.s.* N/A	NNT NNH 17 NNT NNH 20	• Mean age 41 and female 59%, FEV_1 63%PV, non-white ethnicity 13% in FP + SLM group; mean age 40and female 61%, FEV_1 63%PV, non-white ethnicity 17% in FP group; mean age 39 and female 65%, FEV_1 63%PV, non-white ethnicity 11% in TAA group • No detail on randomisation method • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes			Comments
(Aubier et al. 1999) RCT Grade 1+ Country: Netherlands, France	Combination: Fluticasone 500 µg + salmeterol 50 µg bd Diskus inh and placebo bd V Concurrent: Fluticasone 500 µg + salmeterol 50 µg bd Diskus inh and placebo bd V Fluticasone 500 µg bd diskus inh and placebo bd 12 weeks	Inclusion: Age 12-78 yrs ICS 12 weeks prior to run-in and BEC or BDP 1500-2000 µg or FP 750-1000 µg daily 4 weeks prior Symptomatic patients (score ≥2) Patients with FEV_1 50-100%PV PEFR 50-85%PV max PEFR after 15 min with 400 µg salbutamol	503	12 weeks (adj mean difference cf. baseline) (se) Relative to FP plus SLM combination. –ve values indicate higher overall value for combination therapy AM PEFR (l/min) *=90% CI **=95% CI PM PEFR (l/min) *=90% CI **=95% CI 28 weeks Adverse event related to treatment (% patients) Combination Concurrent FP alone	FP plus SLM concurrent -3 (4.3) -10, 4* *P*=.535 -6 (4.3) -13, 1* *P*=.160 17% 14% 19%	FP -21 (4.4) -29, -12** *P*<.001 -21 (4.3) -29, -12** *P*<.001	• Mean age 46 and female 43%, FEV_1 2.44L in FP + SLM combo group; mean age 48 and female 50%, FEV_1 2.32L in FP + SLM concurrent group; mean age 50 and female 47%, FEV_1 2.33L in FP group • Little detail on randomisation, concealment and blinding methodology • Post-randomization 100 patients withdrew, 19% of combo group, 16% of concurrent group and 25% from FP group • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Condemi et al. 1999) RCT Grade 1+ Country: United States	Fluticasone mdi 88 µg bd + Salmeterol mdi 42 µg bd V Fluticasone mdi 220 µg bd 2-4 weeks pre-trial: Fluticasone 88 µg bd and as needed salbutamol Treatment 24 weeks	Inclusion: Age 12-75 yrs FEV_1 40-65%PV or 65-85%PV plus one or more of: ≥4 puffs salbutamol daily, 2 days AM/PM PEFR variance ≥20%, 2+ nights asthma awakenings, 2+ days symptom score ≥2 Exclusion: Current tobacco use Hospital asthma admission previous month	437	24 weeks (cf. baseline) (se) (Change)	FP plus SLM	FP	*P* value	• Mean age 37 and female 62%, FEV_1 2.12L in FP + SLM group; mean age 37and female 60%, FEV_1 2.14L in FP group • No detail on randomisation methodology • Pharmaceutical company funded and supported trial • Study drop out rate 9% in FP + SLM group 14% in FP group
				AM PEFR L/min	+46.5(3.5)	+23.8(3.2)	*P*<.001	
				FEV_1 (L)	0.43 (0.04)	0.33 (0.03)	*P*=.013	
				Symptom free days %	+26%	+10%	*P*<.001	
				Rescue salbutamol use (Mean no. puffs daily)	-2.51(0.17)	-1.55(0.15)	*P*<.001	

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kavuru et al. 2000) RCT Grade 1+ Country: United States	Fluticasone 100 µg plus salmeterol 50 µg bd Diskus inh V Salmeterol 50 µg bd Diskus inh V Fluticasone 100 µg bd Diskus inh V Placebo inh bd 12 weeks	Inclusion: Age 12-70 yrs Patients with FEV_1 40-85%PV and ±15% of the screening FEV_1 Either ICS previous 12 weeks and dose (either BDP 252-420µg daily,TAA 600-1000 µg daily, FP 176 µg daily) previous 4 weeks OR SLM 1+ weeks prior Exclusion: ICS group and 12+ puffs salbutamol daily for 3+ days or SLM group 6+ puffs daily or 3+ days 3+ nighttime awakenings previous 7 days req salbutamol Smoker previous 12 months >10 pack years smoker	356	12 weeks (cf. baseline) FEV_1 (L) mean change (se) Asthma symptom score mean change (se) % days no symptoms mean change (se) Adverse event related to treatment (% patients) (cf. baseline) FEV_1 (L) mean change (se) Asthma symptom score Mean change (se) % days no symptoms mean change (se) Adverse event related to treatment (% patients) (cf. baseline) FEV_1 (L) mean change (se) Asthma symptom score Mean change (se) % days no symptoms mean change (se) Adverse event related to treatment (% patients)	FP plus SLM 0.51(0.05) -0.7(0.11) 22.6(4.59) 3% FP plus SLM 0.51(0.05) -0.7(0.11) 22.6(4.59) 3% FP plus SLM 0.51(0.05) -0.7(0.11) 22.6(4.59) 3%	SLM 0.11(0.06) -0.1(0.1) 8.0(3.29) 35% FP 0.28(0.05) -0.2(0.09) 7.2(4.09) 11% Placebo 0.01(0.07) 0.4(0.10) -3.8(3.01) 49%	*P* Value *P*≤.013 *P*≤.013 *P*≤.013 N/A *P*<.001 *P*≤.025 *P*≤.025 N/A *P*≤.027 *P*≤.013 *P*≤.013 N/A	• Mean age 38 and female 41%, no completing study 83% in FP + SLM group; mean age 37 and female 49%, completion rate 56% in SLM group; mean age 39 and female 48%, completion rate 74% in FP group; mean age 35 and female 49%, completion rate 34% in placebo group • Post-randomization, 21 patients from one site excluded because of poor practice standards. ITT analysis excludes these, small difference (non-quantified) in results if included. • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(van Noord et al. 1999) RCT Grade 1- Country: Netherlands	Low steroid requirement: Fluticasone inh (100 µg bd open) + Fluticasone inh (100 µg bd blind) OR Fluticasone inh (100 µg bd open) + Salmeterol inh (50 µg bd blind) V High steroid requirement: Fluticasone inh (250 µg bd open) + Fluticasone inh (250 µg bd blind) OR Fluticasone inh (250 µg bd open) + Salmeterol inh (50 µg bd blind) Run in: 4 weeks Treatment: 12 weeks	Inclusion: Age 12-75 yrs $FEV_1 \geq 50\%PV$ 10+% increase in FEV_1 PV with 400µg salbutamol mdi or 800 µg inh (3 visits or pre-run in period 4 weeks) Daily symptom score ≥1, or diurnal var in PEFR 15+%, or rescue salbutamol 2+ times daily on 4/14 days run in period Exclusion: Change in asthma medication previous 6 weeks OCS previous 3 months	274	12 weeks PEFR L/min (mean increase cf. baseline) (se) AM PM FEV_1 (L) visit 4 (4 weeks) visit 5 (12 weeks) Odds Ratios (FP high dose plus SLM relative to FP low dose plus SLM) Rescue salbutamol use Day Night Days with symptoms	FP low dose plus SLM +18.6 (3.8) +16.2 (4.0) 2.53 (0.8) 2.47 (0.8)	FP High dose plus SLM N/A N/A 2.45 (0.8) 2.48 (0.9) 1.47 2.19 1.52	*P* value *P*<.001 *P*<.001 *P*=.04 *P*=.18 *P*=.03 *P*<.001 *P*=.04	• Mean age 46 and female 53%, FEV_1 (mean L) 2.33 in FP low dose + SLM group; mean age 47 and female 51%, FEV_1 (mean L) 2.34 in FP high dose group • High and low steroid requirements determined pre-study and at run-in • No detail on randomisation, blinding and concealment methodology • Intention to treat based analysis not evident. Study drop out rate 4% in FP low dose + SLM group 7% in FP high dose group • Several key study results lack data detail • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Jenkins et al. 2000) RCT Grade 1+ Country: 9 countries	Salmeterol disk inh 50 µg + Fluticasone disk inh 250 µg + placebo turb inh bd V Budesonide turb inh 800 µg + placebo disk inh bd 24 weeks	Inclusion: Age 14-80 yrs 4+ weeks pre-study: FEV_1 or PEFR≥ 50-85%PV 15+% increase in FEV_1 or mean AM PEFR≤85% after β-agonist Salbutamol 2+ times daily 2+ daytime symptom score on 4+/7 days Exclusion: Asthma requiring hospitalization previous 4 weeks Smoker ≥10 pack years smoker	353	24 weeks adjusted mean over treatment period (se) AM PEFR L/min PM Median % symptom-free days Adverse events related to treatment (% patients)	FP plus SLM 406 (3.67) 416 (3.14) 60% 14%	BDP 380 (3.81) 398 (3.25) 34% 19%	*P* value *P*<.001 *P*<.001 *P*≤.001 N/A	NNT 4 NNH 20	• Mean age 45 and female 50%, FEV_1 (mean% PV) 68 in FP + SLM group; mean age 48 and female 50%, FEV_1 (mean% PV) 72 in BDP group • International based study (9 countries) • Little detail on randomisation, blinding and concealment methodology • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Pearlman et al. 1999) RCT Grade 1- Country: United States	Placebo mdi bd V Salmeterol mdi 42 µg bd V Fluticasone mdi 88 µg bd V Fluticasone mdi 220 µg bd V Salmeterol mdi 42 µg bd + Fluticasone mdi 88 µg bd V Salmeterol mdi 42 µg bd + Fluticasone mdi 220 µg bd 4 weeks	Inclusion: Age 12-62 yrs FEV_1 50-80%PV 15+% increase in FEV_1 15 min after 180 µg (2 puffs) salbutamol Daily or as needed β-agonists previous 6 months Exclusion: Smoker previous 12 months >10 pack years O/I/IVCS previous 1 month Daily OCS previous 6 months	136	4 weeks	Baseline FEV_1 (L)	Endpoint mean change FEV_1 (L)	*P* value	• Poor comparative baseline demographics between groups • Placebo N=23, mean age 35 and female 57%, Non-Caucasian 9% • SLM (42µg) N=21, mean age 29 and female 33%, Non-Caucasian 0% • FP (88µg) N=23, mean age 27 and female 26%, Non-Caucasian 0%, • FP (220µg), N=23, mean age 32 and female 43%, Non-Caucasian 9% • SLM (42µg) + FP (88µg) N=25, mean age 33 and female 60%, Non-Caucasian 16% • SLM (42µg) + FP (220µg) N=21, mean age 26 and female 33%, Non-Caucasian 19% • Pharmaceutical company funded and supported trial • Study drop out rate 4% in FP low dose + SLM group, 7% in FP high dose group • Several key study results lack data detail
				Placebo	2.39 (0.13)	0 (0.09)		
				SLM (42µg)	2.75 (0.1)	0.29 (0.12)		
				FP (88µg)	2.91 (0.13)	0.27 (0.07)		
				FP (220µg),	2.52 (0.14)	0.30 (0.09)	*P*≤.05*	
				SLM (42µg) + FP (88µg)	2.31 (0.12)	0.59 (0.10)	*P*<.05*^	
				SLM (42µg) + FP (220µg)	2.62 (0.12)	0.75 (0.16)	*P*<.05*^	
				* vs placebo ^ vs SLM 42µg, FP 88µg and FP220µg				
					Baseline	Mean change		
				Asthma symptom score				
				Placebo				
				SLM (42µg)	1.3 (0.2)	-0.2 (0.2)		
				FP (88µg)	1.3 (0.2)	-0.5 (0.1)		
				FP (220µg),	1.2 (0.1)	-0.1 (0.1)	*P*<.05*	
				SLM (42µg) + FP (88µg)	1.3 (0.2)	-0.3 (0.1)		
				SLM (42µg) + FP (220µg)	1.2 (0.2)	-0.8 (0.2)		
					1.1 (0.2)	-0.4 (0.1)	*P*<.05*^	
				* vs placebo ^ vs FP 88µg				

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Weersink et al. 1997) RCT Grade 1- Country: Netherlands	Salmeterol mdi 50 µg bd V Fluticasone mdi 250 µg bd V Fluticasone mdi 250 µg bd + salmeterol mdi 50 µg bd Methacholine challenge (MCh) Or Adenosine 5'mono-phosphate challenge (AMP) To FEV_1 PC_{20} or MCh (19.6mg/ml) or AMP (640mg/ml) 6 weeks	<u>Inclusion:</u> Age 18-45 yrs Circadian variation in PEFR15+% BHR to MCh PC_{20} <9.6 mg/ml IgE elevated to house dust mite (RAST≥2) Short-acting β-agonist on demand previous 4 weeks <u>Exclusion:</u> Smoker Acute asthma exacerbation, OCS previous 8 weeks ICS previous 4 weeks	50	6 weeks Mean Circadian PEFR variation 100*(highest-lowest 24-h value)/mean 24-h value per day over 3 days Baseline End of period FEV_1 (L) (%PV increase cf. baseline) 4 PM (se) 4 AM (se) PC_{20} MCh (se) 4 PM 4 AM	<u>SLM</u> 22.4% 9.1% +10.8% (2.4) +19.6% (3.6) +1.5(0.5) +2.4(0.5)	<u>FP</u> 24.0% 7.9% +7.6% (3.4) +15.9% (3.0) +2.1(0.5) +3.0(0.5)	<u>SLM+FP</u> 24% 10% +5.9% (3.8) +17.9% (3.8) 2.5(0.6) 2.9(0.8)	*P Value* Between *n.s.* Within *P*<.0001 Between *P*=.2 Within *P*=.0001 Between times *P*=.0005 PC_{20} MCh Between *P*=.04 Within *P*<.0001Between times *P*=.1	• Mean age 28 and female 50%, FEV_1 77%PV, in SLM group; mean age 28 and female 56%, FEV_1 88%PV, in FP group; mean age 26 and female 50%, FEV_1 83%PV, SLM + FP group • Baseline differences post-randomisation • Patients recruited from 1 outpatient clinic and newspaper advertisements • No intention to treat analysis, 4 treated patients not included in analysis • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Murray et al. 1999) RCT Grade 1+ Country: United States	Beclomethasone mdi 168 µg bd + salmeterol mdi 42 µg bd V Beclomethasone mdi 336 µg bd 24 weeks	Inclusion: Age 18-82 yrs FEV_1 45-80%PV 12+% increase in FEV_1 PV with 180 µg salbutamol Symptomatic while taking 336 µg beclomethsone or 800 µg triamcinolone daily Constant immunotherapy ok if 12+ weeks Exclusion: Patients on other asthma medication except theophylline, as needed salbutamol and asthma exacerbation medication	514	24 weeks	BDP + SLM	BDP	*P* value	• Mean age 42 and female 59%, FEV_1 65%PV in BDP + SLM group; mean age 42 and female 55%, FEV_1 64%PV in BDP dose group • Pharmaceutical company funded and supported trial • Several key study results (salbutamol use, drug safety) lack data detail • Unclear if intention to treat analysis used
				FEV_1 (L) baseline	2.30	2.31		
				24 weeks (cf. BDP)	2.68	2.54	*P*<.05	
				Symptom score (mean change cf. baseline at 24 weeks)				
				Wheeze	-0.49	-0.27	*P*≤.05	
				Shortness of breath	-0.71	-0.25	*P*≤.05	
				Chest tightness	-0.62	-0.33	*P*≤.05	
				Asthma exacerbations % patients	17%	18%	*n.s.*	

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Kelsen et al. 1999) RCT Grade 1+ Country: United States	Beclomethasone mdi 168 µg bd + Salmeterol mdi 42 µg bd V Beclomethsone mdi 336 µg bd Run-in: 2 weeks Treatment: 24 weeks	Inclusion: Age 18-77 yrs FEV_1 45%-80%PV ≥12% increase in FEV_1 after 180 µg salbutamol ≥3/7 days symptoms, rescue medication in previous week ICS 336 µg daily BDP or 800 µg daily 2 weeks prior Non-smoker	483	24 weeks (mean change over treatment period) Mean AM PEFR L/min Baseline L/min Treatment period L/min Mean PM PEFR L/min Baseline L/min Treatment period L/min % of symptom free days Mean change over 24 weeks (se) % nights with no awakenings (baseline) (se) mean change % nights no salbutamol use baseline (se) mean change n and % patients reporting exacerbations n and % patients with drug related adverse events	BEC+ SLM 389.7 N/A N/A 37.5 23.6% 67.0 (2.3) 18.8 (1.7) 60.2 (2.5) 23.2 (2.0) 38 (16%) 26 (11%)	BEC 390 N/A N/A 14.8 12.5% 68.0 (2.2) 13.4 (1.6) 60.4 (2.4) 14.7 (1.9) 44 (18%) 34 (14%)	*P* value *P*<.001 *P*<.001 *P*≤.05 N/A *P*≤.05 N/A *P*≤.05 N/A N/A	NNT 9	• Mean age 42 and female 57%, FEV_1 65%PV in BEC+SLM group; mean age 42 and female 65%, FEV_1 64%PV in BEC group • Of the 483 patients randomized 20.1% did not complete study. Dropout rates 20% in each treatment arm. Results use ITT based analysis • Some primary PEFR data values are not reported, only *p* values given • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Nathan et al. 1999) RCT Grade 1+ Country: United States	Salmeterol mdi 42 µg bd V Beclomethasone mdi 84 µg Qid V Placebo mdi bd Methacholine challenge (MCh) To FEV_1 PC_{20} or MCh 75 (mg/ml) in neb 26 weeks	Inclusion: Age 12+ yrs FEV_1 65-90%PV 12+% increase in FEV_1 within 30 min of 180 µg salbutamol mdi Daily/as needed β-agonists with no I/OCS previous 6 months Exclusion: Decline in FEV_1 of ≥ 15% after saline inhalation Asthma requiring hospitalization previous 4 weeks	386	26 weeks mean increase (se) over treatment period FEV_1 (L) Salbutamol free nights (mean % increase) Mean increase PD_{20} MCh (se) Week 14 Week 26	SLM 0.28 (0.04) 23% 1.39 (0.24) 1.29 (0.26)	BEC 0.23 (0.04) 23% 1.57 (0.26) 1.42 (0.24)	Placebo 0.08 (0.04) 9% 0.16 (0.22) 0.24 (0.29)	*P* value cf. placebo *P*≤.014 *P*≤.014 *P*<.001 *P*≤.033	• Mean age 31 and female 54%, FEV_1 79%PV, AM PEFR(L/min) 405 in SLM group; mean age 30 and female 57%, FEV_1 78%PV, PEFR(L/min) 394 in BDP group; mean age 29 and female 50%, FEV_1 81%PV, PEFR(L/min) 417 in placebo group • Significantly higher baseline AM PEFR in placebo group • ITT analysis but 81/368 (22%) withdrawals. Across treatment arms 23% SLM, 18% BEC, 22% PLC groups • Data for some primary outcomes not shown • Pharmaceutical company funded and supported trial

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Vermetten et al. 1999) RCT Grade 1- Country: Netherlands	Beclomethasone D-inh 200 µg bd + Salmeterol D-inh 50 µg bd V Beclomethasone diskinh 400 µg bd Run-in: 2 weeks Treatment: 12 weeks	Inclusion: Age 18-66 yrs 6+ weeks prior: ICS BEC/BDP 200-400 µg daily ≥15% reversibility in PEF Exclusion: Asthma exacerbation requiring change to medication in run-in period	233	12 weeks (average of last 2 weeks of treatment period)	BEC+ SLM	BEC	*P* value	• Mean age 42 and female 47%, AM PEFR(l/min) 404, PM PEFR 431 in BEC+SLM group; mean age 42 and female 62%, AM PEFR(l/min) 390, PM PEFR 413 in BEC group • Differences in baseline demographics for % female and AM/PM PEFR values • Of the 233 patients randomized 202 completed study. Whether or not ITT analysis not specified. No detail on randomisation, blinding and concealment methodology. • Treatment endpoints are averages over the last 2 weeks. • Some primary PEFR data values are not reported, only *p* values given • Pharmaceutical company supported trial
				Mean AM PEFR L/min				
				Baseline L/min	404	390		
				Treatment period L/min	N/A	N/A	*P*=.066	
				Mean PM PEFR L/min				
				Baseline L/min	431	413		
				Treatment period L/min	N/A	N/A	*P*=.036	
				Diurnal variation in PEFR%(se)				
				Baseline	9.5% (0.8)	8.8% (0.6)		
				Treatment period	6.6% (0.6)	7.2% (0.7)	*n.s.*	
				(proportion of days with) Asthma symptoms				
				Day Baseline period	0.56 (0.04)	0.54 (0.03)		
				Day Treatment period	0.37 (0.04)	0.38 (0.04)	*n.s.*	
				Night Baseline period	0.43 (0.04)	0.41 (0.03)		
				Night Treatment period	0.33 (0.04)	0.34 (0.04)	*n.s.*	
				Av. No. of blisters per day of rescue medication-baseline	0.88 (0.09)	0.84 (0.09)		
				Treatment	0.48 (0.07)	0.61 (0.10)	*P*<0.05	
				Av. No. of blisters per night of rescue medication-baseline	0.47 (0.06)	0.47 (0.05)		
				Treatment	0.30 (0.06)	0.37 (0.06)	*n.s.*	

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Pauwels et al. 1997) RCT Grade 1+ Country: 9 countries	Run-in period: Budesonide inh 800 µg bd terbutaline 250 µg inh as needed Treatment: Budesonide inh 100 µg bd + placebo inh bd V Budesonide 100 µg inh bd + formoterol inh 12 µg bd V Budesonide inh 400 µg bd + placebo inh bd V Budesonide 400 µg inh bd + formoterol inh 12 µg bd terbutaline 250 µg inh rescue medication Run-in: 4 weeks Treatment: 52 weeks	Inclusion: Age 18-70 yrs Patients with $FEV_1 \geq 50\%$PV and 15+% increase from baseline FEV_1 after inhalation of 1 mg terbutaline Exclusion: Patients taking 2000+ µg daily beclomethasone or 1600+ µg daily mdi or 800+ µg daily budesonide inh 3+ courses OCS or asthma requiring hospitalization previous 6 months	852	52 weeks	Low dose BDP + placebo	Low dose BDP + FRM	High dose BDP + placebo	High dose BDP+ FRM	• Mean age 42 and female 49%, FEV_1 76 in low BDP + placebo group; mean age 41 and female 50%, FEV_1 76 in low BUD + FRM group; mean age 44 and female 52%, FEV_1 76 in high BDP + placebo group; mean age 42 and female 53%, FEV_1 76%PV high BUD + FRM group • International based study (9 countries) • Post-randomisation, 158 patients did not complete study, 44 of these did not fulfil the entry criteria and were incorrectly randomised. Whether ITT analysis not clearly defined • Pharmaceutical company funded and supported trial
				Yearly rate of asthma exacerbations (no/patient/yr)					
				Severe	0.91	0.67	0.46	0.34	
				Mild	35.4	21.3	22.3	13.4	
				Episode free days (mean % of year)	41.7%	51.1%	45.7%	54.8%	
				Asthma symptom score Day	0.57	0.46	0.53	0.33	
				Night	0.37	0.31	0.38	0.20	
				Rescue medication during day no of inhalations	0.91	0.57	0.82	0.44	
						*P V*alue Higher vs lower dose of BDP			
				Yearly rate of asthma exacerbations (no/patient/yr)					
				Severe		*P*<.001			
				Mild		*P*<.001			
				Episode free days (mean % of year)		*P*=.16			
				Asthma symptom score					
				Day		*P*=.01			
				Night		*P*=.01			
				Rescue medication during day (no of inhalations)		*P*<.001			

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Juniper et al. 1999) RCT Grade 1- Country: 5 countries	Run-in period: Budesonide inh 800 µg bd terbutaline 250 µg inh as needed Treatment: Budesonide inh 100 µg bd + placebo inh bd V Budesonide 100 µg inh bd + formoterol inh 12 µg bd V Budesonide inh 400 µg bd + placebo inh bd V Budesonide 400 µg inh bd + formoterol inh 12 µg bd Terbutaline 250 µg inh rescue medication Run-in: 4 weeks Treatment: 52 weeks	Inclusion: Age 18-70 yrs Patients with $FEV_1 \geq 50\%PV$ and 15+% increase from baseline FEV_1 after inhalation of 1 mg terbutaline IGS previous 3+ months with patients taking <2000 µg daily beclomethasone or <1600 µg daily mdi or <800 µg daily budesonide inh	470	52 weeks	High dose BDP+ FRM	*P* Value Cf. other groups	NNT (provided Result)	• Mean age 42 and female 51% in low BDP + placebo group; mean age 42 and female 48% in low BDP + FRM group; mean age 44 and female 51% in high BDP + placebo group; mean age 44 and female 59% in high BDP + FRM group • International based study (9 countries) • Earlier study acknowledgement to (Pauwels et al. 1997) This study's primary outcome measure is asthma quality of life assessment using AQLQ. Clinical results previously reported in earlier study • Post-randomisation, 114/470 (24%) of patients did not complete study after 52 weeks. 4/470 patients did not fill in AQLQ at baseline are excluded from analysis • Insufficient data detail for analysis of AQLQ results • Pharmaceutical company funded and supported trial
				AQLQ total score change	0.21	*P*=.028	11.9	

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Kips et al. 2000) RCT Grade 1- Country: Canada, England, Belgium	Run-in period: Budesonide inh 800 µg bd terbutaline 0.25 mg inh as needed Budesonide 100 µg inh bd + formoterol inh 12 µg bd V Budesonide inh 400 µg bd + placebo inh bd Run-in: 4 weeks Treatment: 52 weeks	Inclusion: Age 18-70 yrs Patients with $FEV_1 \geq 50\%$PV and 15+% increase from baseline FEV_1 after inhalation of 1 mg terbutaline Exclusion: Patients taking 2000+ µg daily beclomethasone or 1600+ µg daily mdi or 800+ µg daily budesonide inh or 800+ µg daily fluticasone inh 3+ course OCS or asthma requiring hospitalization previous 6 months	60	52 weeks	BDP + FRM	BDP + placebo	*P* value	• Mean age 35 and female 59%, ICS µg daily 676, FEV_1 L start run-in 2.87, end run-in 2.93 in BDP + FRM group; mean age 38 and female 61%, ICS µg daily 706.5, FEV_1 L start run-in 2.52, end run-in 2.71 in BDP + placebo group • Differences in baseline FEV_1 (lower in BDP+ placebo group), ICS usage higher here also. Not significant according to study • International based study (3 countries) • Primary efficacy outcome markers of airway inflammation in induced sputum. Only secondary outcomes appraised. Lung function data detail not reported • Whether ITT analysis not clearly defined. No information on study drop out rates during treatment • Pharmaceutical company funded and supported trial
				Yearly rate of asthma exacerbations (no/patient/yr)				
				Severe (se)	0.29 (0.14)	0.47 (0.24)	*n.s.*	
				Mild (se)	18.3 (6.92)	14.6 (5.42)	*n.s.*	
				Episode free days (mean % of year) (se)	41.3% (7.0)	30.4% (6.0)	*n.s.* *n.s.*	
				Mean AM PEFR L/min	N/A	N/A	*n.s.*	
				Mean PM L/min	N/A	N/A	*P*<.05	

Table 18: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Crompton et al. 1999) RCT Grade 1+ Country: 3 European countries	Bambuterol po 10 mg nocte (1 week) 20 mg nocte (5 weeks) + placebo mdi V Salmeterol mdi 50 µg bd + placebo Run-in: 2 weeks Treatment: 6 weeks	Inclusion: Age 18+ yrs 4+ weeks prior: ICS BDP/BEC 800-2000 µg daily other than with turbuhaler or FP/BUD 400-2000 µg daily via turbuhaler or OCS such as prednisone at ≤ 20 mg daily ≥1 nocturnal/early morning awakening req rescue medication ≥15% decr in overnight PEFR on 3/7 days preceding entry Exclusion: Asthma requiring hospitalization Previous 4 weeks	135	6 weeks Median AM PEFR L/min Baseline L/min Treatment period L/min Change from baseline Median change (cf. baseline) Evening PEFR L/min Percent overnight fall in PEFR% Percent nights an awakening % No. puffs rescue medication during day No. puffs rescue medication during night Asthma symptoms, day night	BMB 276 310 50 12 -11% -21% -0.33 -0.28 -0.17 -0.32	SLM 272 327 55 3 -14% -29% -0.57 -0.26 -0.11 -0.32	*P* value N/A N/A *P*=.53 *P*=.82 *P*=.17 *P*=.22 *P*=.24 *P*=.88 *P*=.48 *P*=.57	• Mean age 41 and female 60%, FEV_1 66%PV in BMB group; mean age 41 and female 56%, FEV_1 68%PV in SLM group • International based study (3 countries) • Of the 135 patients randomized 118 completed study. Of the total, 126 patients were considered valid and are included in the analysis. Not strict ITT analysis • Treatment endpoints are calculated during weeks 3 to 6 Both median and mean values calculated and appropriate statistical measures used • Pharmaceutical company funded and supported trial

Table 19: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus leukotriene antagonists) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Malmstrom et al. 1999) RCT Grade 1+ Country: Multinational	Beclomethasone inh 200 µg bd V Montelukast po 10 mg nocte V Placebo 12 weeks	Inclusion: Age ≥ 15 yrs FEV_1 50-85%PV Nonsmoker Exclusion: Pharmaceutical limitations	895		BEC	MNT	95%CI (diff)	NNT	• Median age 35 and female 61% • Mean FEV_1 65%PV • Pharmaceutical company funded and supported trial • Baseline differences in gender mix between interventions which were of uncertain significance • Unclear whether ITT analysis was used
				% Δ am FEV_1	13.1	7.4	3, 8.5		
				% Δ daytime symptom score	-0.62	-0.41	-0.33, -0.09		
				% Δ nocturnal awakenings (n/wk)	-2.4	-1.7	-1.08, -0.32		
							P value		
				Asthma attacks (% patients)	10.1	15.6	*P*<0.05	18	
(Bleecker et al. 2000) RCT Grade 1+ Country: United States	Fluticasone inh 88 µg bd V Zafirlukast po 20 mg bd 12 weeks	Inclusion: Age ≥12 yrs FEV_1 50-80%PV Exclusion: History of life threatening asthma Use of tobacco in past year or >10 pack-years total Resp infection within 2 weeks of screening Pharmaceutical limitations	451		FP	ZAF	*P* value	NNT	• Mean age 41 and female 50% • Mean FEV_1 68%PV • Supported by fluticasone producers
				Δ am FEV_1 (L)	0.42	0.2	*P*<0.001		
				Δ symptom free days (%)	28.5	15.6	*P*<0.001	8	
				Δ rescue free days (%)	40.4	24.2	*P*<0.001	6	
				Δ nights with no awakenings (%)	21.2	8.0	*P*<0.001	8	

Table 19: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus leukotriene antagonists) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Westbroek and Pasma 2000) CO Grade 1+ Country: Netherlands	Fluticasone inh 100 µg bd V Zafirlukast po 20 mg bd 2 weeks each	Inclusion: Age 18-70 yrs $FEV_1 \geq 50\%PV$ Non smoker Exclusion: Resp infection or asthma admission within a month of screening Pharmaceutical limitations	30		FP	ZAF	95%CI (diff)	• Mean age 45 and female 70% • Financial support from producers of fluticasone • No comparison of asthma severity at baseline • Adequate concealment could not be determined
				PC_{20} histamine (mg/ml)	1.61	0.99	0.05, 1.50	
				AM PEFR (L/min)	409	391	-0.08, 35.3	
(Laviolette et al. 1999) RCT Grade 1+ Country: 18 countries	Montelukast po 10 mg nocte + beclomethasone inh 200 µg bd V Beclomethasone inh 200 µg bd V Montelukast po 10 mg nocte V Placebo	Inclusion: Age ≥15 yrs FEV_1 50-85%PV Non-smoker Exclusion: Resp infection within 3 weeks of screening Pharmaceutical limitations	642		BEC/MNT	BEC	*P* value	• Mean age 39 and female 51% • Mean FEV_1 72%PV • Other study comparisons not presented in full • Baseline differences in placebo group from other interventions • Pharmaceutical company funded and supported trial
				% Δ am FEV_1	5.08	0.72	$P < 0.001$	
				Δ daytime asthma symptom score	-0.13	-0.02	$P = 0.04$	
				Δ night awakenings (n/week)	-1.04	-0.45	$P = 0.01$	
				Asthma attacks (% patients)	6.2	12.0	$P = 0.06$	

Table 20: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus short-acting beta-agonist) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Hancox et al. 1999b) CO Grade 1+ Country: New Zealand	Budesonide inh 400 µg bd + terbutaline inh 1000 µg Qid V Budesonide inh 400 µg bd V Terbutaline inh 1000 µg Qid V Placebo 6 weeks each	Inclusion: Age 9-64 yrs Exclusion: Current or ex cigarette smoker (>5 pack years) Pharmaceutical limitations	61		BDP/TEB	BDP	TEB	• Mean age 27 and female 69% • Participants able to tolerate the withdrawal of inh steroid • Pharmaceutical company involved in supplying inhalers and supporting the lead author • No baseline comparison post-randomisation
				Δ AM PEFR (cf. BDP)	14			
				95%CI	5,23			
				Δ am PEFR (cf. TER)	27			
				95%CI	17,37			
				Night awakening (%)	1.9	3.4	4.0	
				P value	*n.s.*	*n.s.*	*n.s.*	
				Rescue medication use (puffs/day)	0.3	0.5	0.5	
				P value	*n.s.*	*n.s.*	*n.s.*	
(Aldridge et al. 2000) CO Grade 1+ Country: New Zealand	Budesonide inh 400 µg bd + terbutaline inh 1000 µg Qid V Budesonide inh 400 µg bd V Terbutaline inh 1000 µg Qid V Placebo 6 weeks each	Inclusion: Age 16-64 yrs FEV_1 > 50%PV Exclusion: Current or ex-cigarette smoker (>5 pack years) Pharmaceutical limitations	34		BDP/TEB	BDP	TEB	• Mean age 39 and female 47% • Mean FEV_1 90%PV • No baseline comparison post-randomisation • 82% of participants randomised were analysed • Pharmaceutical company involved in supplying inhalers and supporting the lead author • Selected from participants in (Hancox et al. 1999b)
				AM PEFR (L/min)	491 *P* =.0011 *P* < .0012	469 *P* = 0.043	450	
				Daytime wheeze (% days present)	4 *n.s.*[1] *P* = .02[2]	9 *n.s.*[3]	18	
				Nighttime wheeze (% days present)	3 *n.s.*[1] *P* = .003[2]	4 *n.s.*[3]	12	
				Rescue med use (Median % days used)	0 *P* =.05[1] *n.s.*[2]	0 *n.s.*[3]	0	
				[1]Combined versus BDP, [2]combined versus TEB, [3]BDP versus TEB				

Table 20: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus short-acting beta-agonist) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Hancox et al. 1999a) CO Grade 1- Country: New Zealand	Budesonide inh 400 µg bd + terbutaline inh 1000 µg Qid V Budesonide inh 400 µg bd V Terbutaline inh 1000 µg Qid V Placebo 6 weeks each	Inclusion: Age 16-64 yrs Exclusion: Current or ex-cigarette smoker (>5 pack years) Pharmaceutical limitations	34	% fall FEV_1 post methacholine (95%CI)	BDP/TEB 25.9 (22.2, 28.2)	BDP 26.1 (22.3, 28.3)	TEB 26.9 (24.4, 28.5)	• Female 47% • Mean FEV_1 90%PV • No baseline comparison post-randomisation • 76% of participants randomised were analysed • Pharmaceutical company involved in supplying inhalers and supporting the lead author • Selected from participants in (Hancox et al. 1999b)

Table 21: Summary of studies investigating the effect of pharmaceuticals (cromoglycate versus inhaled steroid) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Hoshino et al. 1998) RCT Grade 1+ Country: Japan	Ketotifen po 1 mg bd V Disodium cromoglycate (DSCG) inh 2 mg Qid V Beclomethasone inh 100 µg Qid 12 weeks	Inclusion: Age 16-50 yrs 20+% increase in FEV_1 or PEFR Daily/as needed β-agonists with no I/OCS previous 6 months Exclusion: FEV_1 PV < 50% Smoker I/OCS or DSCG in previous 4 months	32	12 weeks Asthma symptoms Median FEV_1 (%PV) Before After Median PEFR(L/min) Before After	Ketotifen 72.0 80.0 *n.s.* 450 500 *n.s.*	DSCG 63.2 72.5 *P*<.05 350 450 *P*<.01	BDP 66.0 74.3 *P*<.05 425 475 *P*<.01	*P* value DSCG v Ketotifen *P*<.01 BDP v Ketotifen *P*<.05 DSCG v Ketotifen *P*<.05 BDP v Ketotifen *P*<.05	• N=13, mean age 27 and female 46%, FEV_1 72%PV, PEFR(l/min) 450 in ketotifen group; N=9, age 26 and female 33%, FEV_1 63%PV, PEFR(l/min) 350 in DSCG group; N=9, age 30 and female 30%, FEV_1 66%PV, PEFR(l/min) 425 in BEC group • Small numbers in study treatment arms. Baseline differences in FEV_1 PV% and PEF • The study also included analysis of fibreoptic bronchoscopy and immunohistochemistry data

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Raphael et al. 1999) RCT Grade 1+ Country: United States	Fluticasone inh 88 µg bd, 220 µg bd V Beclomethasone inh 168 µg bd, 336 µg bd 12 weeks	Inclusion: Age ≥ 12 yrs FEV_1 45 – 80%PV Inh steroids 6 mths prior to study Exclusion: Pharmaceutical limitations	399		FP 88	BEC 168	FP 220	BEC 336	• Mean age 39 and female 59% • Mean FEV_1 65%PV • Financial support from the producers of both drugs
				Δ FEV_1 (L)	0.31 *P* = .048 (cf. Beclo168)	0.18	0.36 *P* = .034 (cf. Beclo336)	0.21	
				Δ Night awakenings	-0.03 *n.s.* (cf. Beclo168)	-0.03	-0.12 *n.s.* (cf. Beclo336)	-0.07	
				Δ % days with no symptoms	14.0 *P* = .03 (cf. Beclo168)	4.9	8.7 *P* = .03 (cf. Beclo336)	4.4	
(Pauwels et al. 1998) CO Grade 1+ Country: Belgium	Fluticasone inh 0.5 BEC dose V Beclomethasone inh 1 mg, 1.5 mg, 2 mg dose daily[1] 6 months on each	Inclusion: Age 18-75 years FEV_1 ≥ 40%PV PO steroids for <6 weeks during past year Exclusion: Change in asthma medication, asthma hospitalisation or resp infection in past month Pharmaceutical limitations	340		FP	BEC	*P* value		• Mean age 46 and female 42% • Mean FEV_1 80%PV • Bone density measured in 61% of randomised population • Difference in duration of inhaled steroid group between the two study ord groups • Supported by the produce of fluticasone • [1]Dose set by response to ru in meds
				Serum cortisol (µg%)	13.3	13.3	*n.s.*		
				Serum osteocalcin (ng/ml)	1.72	1.54	*P* < .001		
				Δ lumbar spine density (%)	1%	0%	*P* = 0.05		
				QoL score	1.22	1.20	*P* < 0.05		

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Egan et al. 1999) RCT Grade 1- Country: United Kingdom	Fluticasone inh 500 µg bd V Beclomethasone inh 1000 µg bd 2 years	Inclusion: Age 18-50 years (Males), 18-40 years (Female) Regular beclomethasone or budesonide treatment at 1000-2000 µg daily	33		FP	BEC	Adjusted diff (95%CI)	• Mean age 35 and female 52% • Mean inhaled steroid dose 1390 µg daily • 73% completed the study • Mineral density assessed by dual energy CT scan • No statistical analysis of difference in PEFR • Study funded by fluticason producer
				Vertebral trabecular bone mineral density (mg/cm3)	161	148	14 (1-26)	
				PEFR (L/min)	431	513	N/A	

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Malo et al. 1999) CO Grade 1- Country: Canada	Fluticasone inh (0.5 BEC dose) V Beclomethasone inh 4 mths each	Inclusion: Age >18 yrs $FEV_1 \geq 15\%$ increase post bronchodilator Exclusion: No po steroids continuously for >1 year in the past 5 Tobacco use within 1 year Pharmaceutical limitations	69		FP	BEC	*P* value		• Mean age 48 and female 57% • Mean FEV_1 76%PV • No baseline comparison post-randomisation • Concealment method not described • ITT analysis not clear • Pharmaceutical company producing fluticasone funded and supported trial
				Asthma exacerbation (%)	13	12	*P* = 0.4		
				≥1 night awakening (%)	22	14	*P* = 0.3		
				Cortisol change post cortrosyn (µmol/dL)	422	357	*P* = .005		
				Skin bruising score	1.24	1.64	*P* = .04		
				Serum osteocalcin (ng/ml)	3.5	2.8	*P* = .003		
(Heinig et al. 1999) RCT Grade 1+ Country: 4 countries	Fluticasone d-inh 2000 µg daily V Budesonide turbuhaler 2000 µg daily 24 weeks	Inclusion: Age 18-75 yrs $FEV_1 \geq 15\%$ increase post bronchodilator Exclusion: Pharmaceutical limitations	395		FP	BDP	*P* value	NNT	• Mean age 48 and female 49% • Supported financially by producers of fluticasone • Methods used to measure outcomes poorly described
				Symptom free days (%)	31.5	22.8	*P* = 0.02	11	
				Days free from rescue medication use (%)	42.7	33.7	*P* = 0.02	11	
				Participants with no asthma exacerbation (%)	60	68	*n.s.*		

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Ringdal et al. 2000) CO Grade 1- Country: Sweden, Norway	Fluticasone inh 800 µg bd V Budesonide inh 800 µg bd 2 weeks each	Inclusion: Age 18-75 yrs $FEV_1 \geq 50\%PV$ Exclusion: Resp infection within 4 weeks of visit 1 Pharmaceutical limitations	48		FP	BDP	*P* value		• Mean age 50 and female 29% • Mean FEV_1 77%PV • No information concerning differences between groups at baseline • Staff employed by the pharmaceutical company producing fluticasone included in the study authors
				AUC serum cortisol (nmol/L)	783	791	*n.s.*		
(Steinmetz 1997) RCT Grade 1- Country: Germany	Fluticasone inh 250 µg bd V Budesonide inh 600 µg bd 6 weeks	Inclusion: Age 18-70 years FEV_1 50-80%PV Indication for treatment with inh steroid but no use of steroids within 3 weeks of study commencement	457		FP	BDP	*P* value	NNT	• Mean age 47 and female 51% • Unblinded study • No mention of pharmaceutical company involvement but the funding source was not stated
				Δ AM PEFR (L/min)	45	34	$P < 0.01$	5	
				Days without asthma symptoms	40	34	$P < 0.05$		
				Patients with adverse events judged as due to study medication	2	6	*n.s.*		
(Berkowitz et al. 1998) RCT Grade 1+ Country: United States	Beclomethasone mdi 168 µg bd V Triamcinolone mdi with extender 400 µg bd 8 weeks	Inclusion: Age 18-65 years FEV_1 50-90%PV Exclusion: Resp infection within 30 days Admission to ICU for asthma or admissions for severe asthma exacerbation in the past Pharmaceutical limitations	339		BEC	TAA	*P* value		• Mean age 38 and female 63% • Baseline difference in age with older mean age in the triamcinolone group • Pharmaceutical company funded and supported trial
				Patients having adverse events (%)	50.0	57.4	*n.s.*		
				Δ FEV_1 (L)	0.27	0.22	*n.s.*		

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Bronsky et al. 1998) RCT Grade 1+ Country: United States	Beclomethasone inh 336 µg daily V Triamcinolone inh 800 µg daily V Placebo 8 weeks	Inclusion: Age 18-65 years FEV_1 50-90%PV Exclusion: Smoking history Resp infection within 30 days Recurent admission for severe asthma exacerbation Pharmaceutical limitations	328	BEC / TAA / *P* value % Δ FEV_1: 11.95 / 7.04 / *P* = 0.08 Mean Δ asthma score: -1.37 / -0.58 / *P* = 0.03	• Mean age 37 and female 53% • Pharmaceutical company funded and supported trial • 75% of participants had outcomes measured at 8 weeks.
(Bateman et al. 2000) RCT Grade 1- Country: Six countries	Triamcinolone HFA inh 450 µg bd V Beclomethasone CFC inh 500 µg bd 12 weeks	Inclusion: Age ≥18 years FEV_1 60-90%PV Exclusion: History of life threatening asthma Recent hospitalisation or acute exacerbation requiring po steroid Current smoker Pharmaceutical limitations	284	TAA / BEC / Diff / 95%CI % Δ AM PEFR: 5.6 / 3.8 / 1.8 / -2.5, 6.1 % Δ FEV_1: 5.4 / 4.5 / 0.9 / -3.1, 4.9 *P* value Δ rescue med use (puffs/day): -0.67 / -0.11 / *P*=0.04 Δ Night awakening: -0.16 / -0.14 / *P*=0.83	• Mean age 43 and female 53% • Mean FEV_1 76%PV • Unblinded study • Note difference in propellants • Triamcinolone producer funded and supported trial

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Condemi et al. 1997) RCT Grade 1+ Country: United States	Fluticasone d-inh 250 µg bd V Triamcinolone inh 200 µg Qid V Placebo 24 weeks	Inclusion: Age ≥ 12 yrs FEV_1 50-80%PV One documented emergency care visit within the past year for asthma exacerbation Exclusion: Pharmaceutical limitations	291		FP	TAA	*P* value	NNT	• Mean age 36 and female 51% • Mean FEV_1 67%PV • Pharmaceutical producers of fluticasone funded and supported trial • Lack of consistency between rescue free days and symptom free days
				Δ AM FEV_1	0.27	0.07	*P* < 0.05		
				Δ salbutamol use (puffs/day)	-0.9	-0.2	*P* < 0.05		
				Δ rescue free days (%)	14	1	*P* < 0.05	8	
				Δ night awakening	-0.03	-0.01	*n.s.*		
				Δ symptom free days (%)	14	12	*n.s.*		
				oropharyngeal candidiasis (%)	8	3	*n.s.*		

Table 22. Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Newhouse et al. 2000) RCT Grade 1- Country: Canada	Flunisolide inh 750 µg bd V Budesonide inh 600 µg bd 6 weeks	Inclusion: Age 18-75 years FEV_1 40-85%PV Requiring a dose of inhaled steroid between 800 and 2000 µg daily Exclusion: Hospital admission for asthma within 6 weeks Upper resp infection within 30 days Pharmaceutical limitations	154		FNS	BDP	*P* value	• Mean age 43 and female 58% • Mean FEV_1 81%PV • Blinding and concealment status not documented • Significant baseline difference in FEV_1 %PV between randomised groups • 80% power to detect 33% difference in cortisol level ($\alpha = 0.05$)
				Δ FEV_1 (%PV)	-2.4	-0.5	*P* = 0.4	
				Δ salbutamol use (puffs/day)	0.4	0.1	*P* = 0.3	
				Nocturnal awakenings (n/night)	0.1	0.1	*P* = 0.9	
				Asthma symptom score	0.1	0.1	*P* = 0.9	
				% patients with oropharyngeal *Candida*	35	42	*P* = 0.4	
				Δ plasma cortisol (µg/L) in Cortrosyn Stimulation Test (higher number = less adrenal suppression)	12.5	10.5	*P* = 0.05	
(McFadden et al. 1999) RCT Grade 1+ Country: United States	Budesonide inh 400 µg mane for 6 weeks followed by 200 µg mane for 12 weeks V Budesonide inh 200 µg mane V Placebo	Inclusion: Age 18-70 years $FEV_1 \geq 80\%$PV if taking steroids or 60-90%PV if not taking steroids Exclusion: Hospital admission for asthma within 2 months Current smoking	309		BDP400	BDP200	*P* value	• Mean age 37 and female 67% • FEV_1 82%PV • Pharmaceutical company funded and supported trial • Identical intervention for last 12 weeks of study so low power to detect a difference
				Δ FEV_1 (L)	0.11	0.10	*n.s.*	
				Δ day symptom scores	-0.36	-0.23	*n.s.*	
				Δ rescue salbutamol use (puffs/day)	-1.09	-1.11	*n.s.*	
				QoL scores	5.55	5.26	*n.s.*	

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Foresi et al. 2000) RCT Grade 1+ Country: Italy	Budesonide inh 100 µg bd +200 µg bd following exacerbation V Budesonide inh 100 µg bd +placebo following exacerbation V Budesonide inh 400 µg bd +placebo following exacerbation 6 months	Inclusion: Age 18-65 yrs FEV_1 50-90%PV Daily inh β-agonist use Exclusion: Current and ex smokers Pharmaceutical limitations	209		BDP 400 + Placebo	Bud 100 + Placebo	*P* value	NNT	• Mean age 39 and female 37% • Mean FEV_1 74%PV • All participants received budesonide 800 µg bd for 1 month prior to randomisation • Financial support from pharmaceutical company • Method of randomisation unclear
				Participants with ≥1 exacerbation (%)	16.9	32.4	*P* = 0.04	6	
					BDP 400 + Placebo	BDP 100 + BDP200			
				Participants with ≥1 exacerbation (%)	16.9	18.7	*n.s.*		
					BDP 100 + BDP200	BDP 100 + Placebo			
				Participants with ≥1 exacerbation (%)	18.7	32.4	*n.s.*		
(Kemp et al. 1999) RCT Grade 1+ Country: United States	Budesonide inh 400 µg bd V Budesonide inh 200 µg bd V Placebo 12 weeks	Inclusion: Age 18-70 years FEV_1 50-80%PV Asthma symptoms on at least 7 of 14 days pre-randomisation Exclusion: Hospital admission for asthma within a month Pharmaceutical limitations	273		BDP 200	BDP 400	*P* value		• Mean age 39 and female 45% • Mean FEV_1 67%PV • Efficacy also studied but no absolute numerical figures provided for these comparisons • Pharmaceutical company involvement not mentioned but no funding source documented • Lack of demographic data in baseline comparison • Method of randomisation not described • Study power not stated
				% patients with normal basal cortisol at baseline and abnormal post-treatment	1	3	*n.s.*		
				% patients with normal stimulated cortisol at baseline and abnormal post-treatment	3	3	*n.s.*		

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Miyamoto et al. 2000) RCT Grade 1+ Country: Japan	Budesonide inh 400 µg bd V Budesonide inh 200 µg bd V Budesonide inh 100 µg bd V Placebo 6 weeks	Inclusion: Age adult PEFR 50-80%PV Exclusion: Steroid use within 1 month Resp infection within 4 weeks	267		BDP 800	BDP 400	BDP 200	*P* value	• Mean age 51 and female 47% • Baseline differences in gender distribution, treatment scores and asthma scores (*P* = 0.05-0.10) • Lack of clarity in some outcome measurements • Some of the study authors were employed by the producer of budesonide
				Δ PEFR (L/min)	71	53	45	*P* < .05 (800 V 200)	
				Physician assessment of significant improvement	76%	73%	57%	*P* < .001 (dose response)	
(Herjavecz et al. 1999) RCT Grade 1+ Country: Hungary and Spain	Budesonide inh 400 µg qd V Budesonide inh 200 µg bd 6 weeks	Inclusion: Age 17-67 years PEFR ≥ 70%PV Exclusion: Asthma exacerbation within 2 months Resp infection within 4 weeks Pharmaceutical limitations	181		qd	bd	Diff (95%CI)		• Mean age 31 and female 59% • Mean FEV_1 93%PV • 80% power to detect a difference of 22 L/min in PEFR (α = 0.05) • Symptom scores higher in bd treatment group at baseline
				Δ FEV_1 (L)	0.03	0.06	-0.03 (-0.11, 0.06)		
				Δ β-agonist use (puffs/day)	0.46	0.38	0.08 (-0.13, 0.28)		

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Tukiainen et al. 2000) RCT Grade 1+ Country: Finland	Budesonide inh 400 µg bd V Budesonide inh 100 µg bd 3 months	Inclusion: Age ≥ 18 yrs Newly detected asthma PC_{20} histamine ≤ 8 mg/ml Exclusion: Pharmaceutical limitations	101	BDP 200 / BDP 800 / *P* value Δ FEV_1 (%PV): 1.7 / 0.6 / *n.s.* Δ asthma symptom score (day): -0.49 / -0.47 / *n.s.* Δ asthma symptom score (night): -0.20 / -0.24 / *n.s.* Δ β-agonist inhalation (day): -0.62 / -0.68 / *n.s.* Δ β-agonist inhalation (night): -0.22 / -0.24 / *n.s.*	• Mean age 39 and female 65% • Mean FEV_1 87%PV • Baseline difference in gender distribution between the two study groups (Female %: Bud 200 – 58, Bud 800 – 72) • Study material and equipment supplied by the producers of budesonide • Study had 90% power to detect a one dose step difference in histamine PC_{20}

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(van der Molen et al. 1998) RCT Grade 1+ Country: Netherlands	One month: Budesonide inh 400 µg bd V Budesonide inh 100 µg bd Both followed by Budesonide inh 200 µg daily Total duration 13 weeks	Inclusion: Age 18-50 yrs FEV_1 > 50%PV Required ≥ 3 doses bronchodilator per week for the month before enrolment Exclusion: >20 pack-years tobacco Asthma exacerbation within 2 months of enrolment Pharmaceutical limitations	84		BDP400	BDP100	*P* value		• Mean age 32 and female 56% • Mean FEV_1 84%PV • Numerical values for PEFR and symptom score not presented at 13 weeks but no statistically significant difference between groups • Unclear whether the drop outs (25%) were included in the analysis therefore the potential for low study power exists • Financial support from budesonide producer
				Δ AM PEFR at 4 weeks (L/min)	27	38	*n.s.*		
				Δ symptom score at 4 weeks	-0.5	-0.6	*n.s.*		
				% Δ bronchodilator use (13 weeks)	-38	-48	*n.s.*		
(Busse et al. 1998) RCT Grade 1+ Country: United States	Budesonide inh 800 µg bd V Budesonide inh 400 µg bd V Budesonide inh 200 µg bd V Budesonide inh 100 µg bd V Placebo 12 weeks	Inclusion: Age 18-70 years FEV_1 40-75%PV Used inhaled steroid for the past 6 months Exclusion: Pharmaceutical limitations	473		100bd	200bd	400bd	800bd	• Mean age 44 and female 54% • Mean FEV_1 65%PV • Financial support from the producers of budesonide • Unclear if ITT analysis was performed
				Withdrawal due to exacerbation (%)	20	11	8	7 (*P*<.01 cf. 100bd). NNT 8	
				Day symptom score	-0.19	-0.24	-0.31	-0.24	
				Rescue med use (puffs/day)	0.72	-1.47	-1.48	-1.50	
				Stimulated cortisol levels (nmol/L)	-3	+6	-7	-7.5	

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Chisholm et al. 1998) RCT Grade 1- Country: Netherlands	Budesonide inh 200 µg qd V Budesonide inh 100 µg bd 8 weeks	Inclusion: Age 18-70 years Postbronchilator FEV_1 >70%PV Exclusion: Acute asthma exacerbation or lower resp infection within 2 months Pharmaceutical limitations	76		qd	bd	*P* value	• Mean age 41 and female 59% • Mean FEV_1 86%PV • Study aimed to determine equivalence of the two dosing regimens. The power of the study was unclear. • Patients were monitored by their own GP • Funding and support was provided by the pharmaceutical company producing budesonide
				Δ AM PEFR (L/min)	1.7	4.3	*n.s.*	
				Δ rescue med use (day)	.02	-0.21	*n.s.*	
				Δ rescue med use (night)	.06	-0.01	*n.s.*	
				Δ symptom score (day)	-0.07	-0.06	*n.s.*	
				Δ symptom score (night)	.02	-0.1	*n.s.*	
(Campbell et al. 1998) RCT Grade 1- Country: United Kingdom and Ireland	Budesonide 400 µg bd for 6 wks followed by 400 µg nocte for 12 wks V Budesonide 400 µg nocte for 18 weeks	Inclusion: Age ≥ 12 years Asthma symps in 2 of past 7 days (prior to study entry) Exclusion: PEFR < 60%PV Pharmaceutical limitations	682		BDP bd initially	BDP nocte	*P* value	• Mean age 33 and female 56% • Double blind for the first 6 weeks followed by open design • Higher drop out rate than expected (10% expected, 33% actual) resulted in not meeting the 80% power target • Sponsored by budesonide producers
				Δ cough score (6 wks)	-0.47	-0.42	*n.s.*	
				Δ cough score (18 wks)	-0.54	-0.49	*n.s.*	
				Δ wheeze score (6 wks)	-0.58	-0.48	*n.s.*	
				Δ wheeze score (18 wks)	-0.70	-0.59	*n.s.*	
				Δ SOB score (6 wks)	-0.62	-0.55	*n.s.*	
				Δ SOB score (18 wks)	-0.68	-0.71	*n.s.*	
				Δ sleep disturbance (n/wk) (6 wks)	-1.04	-0.86	*n.s.*	
				Δ sleep disturbance (n/wk) (18 wks)	-1.21	-1.06	*n.s.*	

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Mahajan et al. 1997) RCT Grade 1+ Country: United States	Fluticasone inh 250 µg bd V Fluticasone inh 100 µg bd V Fluticasone inh 50 µg bd V Placebo 12 weeks	Inclusion: Age ≥ 12 years FEV_1 50-80%PV Exclusion: Pharmaceutical limitations	342		FP100	FP250	FP50	*P* value	• Mean age 35 and female 39% • Pharmaceutical company producing fluticasone funded and supported trial • Inconsistent dose response relationship in the results produces uncertainty about the study
				Living with asthma score (low = improved control)	0.98	1.10	1.12	*P* < 0.05 (F100 V F250 + F100 V F50)	
				Night awakenings (n/week)	0.2	0.4	0.2	*n.s.*	
(Nathan et al. 2000) RCT Grade 1+ Country: United States	Fluticasone inh 500 µg daily V Fluticasone inh 200 µg daily V Fluticasone inh 100 µg daily V Placebo	Inclusion: Age 18-50 yrs FEV_1 > 50%PV Required ≥ 3 doses bronchodilator per week for the month before enrolment Exclusion: >20 pack-years tobacco Asthma exacerbation within 2 months of enrolment Pharmaceutical limitations	330		FP 500	FP 200	*P* value	• Mean age 37 and female 42% • Mean FEV_1 63%PV • Pharmaceutical company producing fluticasone funded and supported trial • Other comparisons with fluticasone 100 µg daily dosage also presented in paper but no significant differences in the presented outcomes
				Δ AM FEV_1 (L)	0.30	0.27	*n.s.*		
				Δ asthma symptom score	-0.25	-0.20	*n.s.*		
				Δ salbutamol use (puffs/day)	-0.90	-0.19	*P* ≤ 0.05		
				Δ night awakenings (n/night)	-0.03	-0.05	*n.s.*		

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Westbroek et al. 1999) RCT Grade 1+ Country: 19 countries	Fluticasone neb 2 mg bd V Fluticasone neb 0.5 mg bd V Placebo 12 weeks	Inclusion: Age ≥ 17 yrs Continuous po steroid for 3 mths before study Exclusion: Changes in asthma medication, resp infection requiring antibiotics or hospital admission for resp disease in past 4 weeks	301		2 mg bd	0.5 mg bd	*P* value	NNT	• Female 45% • 85% on inhaled steroid • Pharmaceutical company funded and supported trial • Higher withdrawal rate in 0.5 mg group
				Median reduction po steroid dose (%)	66.7	50.0	*n.s.*		
				AM PEFR (L/min)	281	291	*n.s.*		
				Nights not awoken (%)	87	74	*P* = 0.05	7	

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Boulet et al. 2000) RCT Grade 1- Country: 8 countries	Fluticasone inh 500 µg mane V Fluticasone inh 250 µg bd 12 weeks	Inclusion: Age ≥ 12 years FEV_1 60-90%PV Previously received beclomethasone 400-1200 µg daily (or equivalent) No changes in asthma medication in past 4 weeks Exclusion: Resp infection or ED therapy in past 4 weeks	443		bd	Mane	90%CI	• Mean age 36 and female 55% • Pharmaceutical company funded and supported trial • Patients excluded from one centre due to poor data quality • ITT analysis not used • [1] Outcome not equivalent
				Δ AM PEFR (L/min)	16.7	0.7	-20.5, -11.1[1]	
				Δ PM PEFR (L/min)	10.4	4.9	-9.7, -1.3	
				Δ FEV_1 (L)	0.08	0	-0.14, -0.01	
							P value	
				Δ day symptom score	-0.26	-0.08	*P* = 0.025	
				Δ night symptom score	-0.07	0.13	*P* < 0.001	
				Δ day rescue med use	-0.25	-0.10	*n.s.*	
				Δ night rescue med use	-0.11	0.05	*P* = 0.003	
(Boulet et al. 2000) RCT Grade 1- Country: 8 countries	Fluticasone inh 200 µg mane V Fluticasone inh 100 µg bd 12 weeks	Inclusion: Age ≥ 12 years FEV_1 70-90%PV Previously received beclomethasone up to 500 µg daily (or equivalent) No changes in asthma medication in past 4 weeks Exclusion: Resp infection or ED therapy in past 4 weeks	461		bd	Mane	90%CI	• Mean age 38 and female 55% • Pharmaceutical company funded and supported trial • ITT analysis not used • [2] Outcomes equivalent between dose regimens by authors pre set criteria although the null hypothesis (no statistically significant difference in outcome) was rejected • Same study as one above.
				Δ AM PEFR (L/min)	18.7	10.5	-13.6, - 2.8[2]	
				Δ PM PEFR (L/min)	13.2	9.7	-8.3, -1.6	
				Δ FEV_1 (L)	0.12	0.07	-0.12, -0.02	
							P value	
				Δ day symptom score	-0.23	-0.25	*n.s.*	
				Δ night symptom score	-0.09	-0.03	*n.s.*	
				Δ day rescue med use	-0.23	-0.23	*n.s.*	
				Δ night rescue med use	-0.17	-0.06	*n.s.*	

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Busse et al. 1999b) RCT Grade 1+ Country: United States	Beclomethasone inh 800 μg daily V Beclomethasone inh 400 μg daily V Beclomethasone inh 100 μg daily (Both HFA and CFC propellants) 6 weeks	Inclusion: Age > 18 years FEV_1 45-75%PV (between run in and randomisation) Exclusion: Smoking within the previous 12 months or > 15 pack-years smoking Upper resp infection within 4 weeks or lower resp infection within 6 weeks	323		BEC 800	BEC 400	BEC 100	*P* value (trend)	• Female 61% • Mean FEV_1 53%PV • Pharmaceutical company producing beclomethasone (HFA propellant) funded and supported trial • Results refer to HFA propellant only. There were similar differences between doses in the CFC propellant group as those presented for HFA propellant.
				Δ am PEFR (L/min)	61.9	49.9	39.1	*P* < 0.05	
				β-agonist use (puffs/day)	3.7	4.5	4.8	*P* < 0.05	
				Nights free from asthma related disturbance (%)	84.0	74.0	77.1	*n.s.*	
(Hampel et al. 2000) RCT Grade 1+ Country: United States and France	Beclomethasone inh HFA 100 μg bd V Beclomethasone inh HFA 50 μg bd V Placebo 6 weeks	Inclusion: Age 18-65 years FEV_1 65-85%PV No steroids for 3 months Nonsmoker Exclusion: Pharmaceutical limitations	270		100bd	50bd	*P* value		• Mean age 34 and female 57% • Mean FEV_1 76%PV • Concealment methods not described • Labelled as blind but no information on single or double • Financial support from producers of beclomethasone • 90% power to detect a clinically significant difference in outcome between placebo and active doses
				Δ FEV_1 (%PV)	8.6	6.7	*n.s.*		
				Δ nights without sleep disturbance (%)	25.2	21.4	*n.s.*		
				Δ daily β-agonist use (n/day)	-1.04	-1.19	*n.s.*		

Table 22: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus inhaled steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(ZuWallack et al. 1997) RCT Grade 1+ Country: United States	Flunisolide inh 500 µg bd V Flunisolide inh 1000 µg mane V Flunisolide inh 1000 µg nocte V Flunisolide inh 500 µg mane 12 weeks	Inclusion: Age 6-70 years $FEV_1 \geq 80\%PV$ Regular use of inhaled steroids and clinically stable after 4 weeks flunisolide 500 µg bd Non smoking ≥ 1 year and < 10 pack-years total	366		500bd	1000mane	1000nocte	500mane	• Mean age 30 and female 55% • Funded by the pharmaceutical producers of flunisolide • Method of randomisation unclear
				Δ daytime symptoms	0.00	0.06	-0.04	0.21 *P*=.0002 (bd) *P*=.002 (mane) *P*=.0001 (nocte)	
				Δ night symptoms	0.00	0.06	-0.03	0.15 *P*=.003 (bd) *P*=.02 (mane) *P*=.002 (nocte)	
				Δ FEV_1 %PV	-2.1	-3.5	-0.7	-4.5 *P*=.03 (bd) *P*>.05 (mane) *P*=.01 (nocte)	
(Pincus et al. 1997) RCT Grade 1- Country: United States	Triamcinolone inh 200 µg Qid V Triamcinolone inh 800 µg at 5.30PM V Triamcinolone inh 800 µg at 8 AM 4 weeks	Inclusion: Age 20-68 years FEV_1 50-85%PV Exclusion: Smoking within 5 years Upper resp infection within 4 weeks Pharmaceutical limitations	60		Qid	5.30pm	8.00am	*P* value	• Mean age 33 and female 46% • No description of concealment or blinding • Unclear whether ITT analysis was used • Funded by pharmaceutical company
				% Δ FEV_1	21.1	15.2	14.7	*n.s.*	
				Δ AM PEFR (L/min)	46	13	-2	*P* = 0.005 (Qid v 8) *P* = 0.05 (5.30 v 8)	
				Δ β-agonist use (puffs/day)	-2.3	-1.3	-1.6	*n.s.*	
				Δ night awakening	-3.0	-2.0	-1.0	*n.s.*	
(Lipworth 1999) SR Grade 1-	Adverse effects of inhaled steroids. Comparison between steroids	Inclusion: RCTs Route of drug administartion documented	21 studies		FP	BEC	TAA	BDP	• No demographic details • Limited database search • No assessment of study quality
				Urinary cortisol suppression (slope gradient)	63.2	32.5	17.3	14.7	
				95%CI cf. fluticasone		(1.0, 60.6)	(3.7, 88.1)	(20.9, 76.1)	

Table 23: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus oral steroids) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Meijer et al. 1999) RCT Grade 1+ Country: Netherlands	Fluticasone D-inh 2000 µg daily V Fluticasone D-inh 500 µg daily V Prednisolone po 30 mg daily 2 weeks	Inclusion: Age 18-56 yrs PC_{20} methacholine ≤ 8 mg/ml Exclusion: Exacerbation of asthma requiring prednisolone Pharmaceutical limitations	120		FP 2000	FP 500	Pred	*P* value	• Median age 27 and female 66% • Mean FEV_1 80%PV • Fluticasone 2000 is a high dose • Financial support from fluticasone producer • Randomisation methodology provided in detail
				Δ FEV_1 %PV	6.5	6.3	4.4	*P* = .13	
				Serum cortisol (nmol/L)	-155	0.0	-118	*P* = .005 (Pred + Flu2000 v Flu500)	
				Rescue med (n/day)	0.0	0.0	0.57	*P* ≤ .05 (Pred V both Flu doses)	
(Li et al. 1999) RCT Grade 1- Country: United States	Fluticasone inh 220 µg bd V Fluticasone inh 88 µg bd V Triamcinolone inh 400 µg Qid V Triamcinolone inh 200 µg Qid V Prednisone po 10 mg daily V Placebo 4 weeks	Inclusion: Age 18-50 yrs FEV_1 ≥ 50%PV Exclusion: Pharmaceutical limitations	128		FP 88/220	TAA 200/400	Pred	*P* value	• Mean age 31 and female 30% • Mean FEV_1 86%PV • ITT analysis not used • All aspects of the study (including financial support) assisted by fluticasone producer
				%Δ 8 hour cortisol (AUC)	-2.6%/-5.7%	-6.4%/ -13.0%	-32.5%	*P* ≤.001 (FP + TAA V PRED)	

Table 23. Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus oral steroids) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Aaronson et al. 1998) RCT Grade 1- Country: United States	Budesonide inh 1600 μg bd V Budesonide inh 800 μg bd V Budesonide inh 400 μg bd V Prednisone po 10 mg daily V Placebo 6 weeks	Inclusion: Age 18-65 yrs $FEV_1 \geq 65\%PV$ Exclusion: Hospitalisation for asthma in past 4 weeks Resp infection in past 4 weeks Corticosteroid therapy within 6 months	64	Δ postcosyntropin plasma cortisol (nmol/L) (P values compared with prednisone)	BDP1600 -90 *P*=0.03	BDP800 -137 *P*=0.08	BDP3200 -249 *n.s.*	Pred -292	• Mean age 31 and female 23% • ITT analysis not used • Budesonide turbuhaler producer funded and supported trial

Acute asthma

Table 24: Summary of studies investigating the effect of pharmaceuticals (steroids) in acute asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Rowe et al. 1999) RCT Grade 1+ Country: Canada	Budesonide inh 1600 µ g daily + Prednisone po 50 m g daily V Prednisone po 50 m g daily 3 weeks	Inclusion: Age 16-60 yrs PEFR < 80%PV Exclusion: Oral or inhaled steroid within 1 week of ED presentation	188		BDP + Pred	Pred	*P* value	NNT	• Mean age 28 and female 61% • Mean PEFR 50%PV • Inhalers supplied by company producing budesonide • Baseline difference in sex, age and severity (the latter favouring prednisone alone)
				Relapse within 21 days (%)	12.8	24.5	*P* = .05	9	
				QoL score	5.9	5.2	*P* = .001		
				FEV_1 %PV	79	79	*n.s.*		
				β-agonist activation (%)	2.4	4.2	*P* = .01		
				Night awakening (mean)	6.2	5.4	*P* = .001		
								NNH	
				Hoarseness (%)	25	46	*P* = .02	5	
				Sore throat (%)	22	41	*P* = .02	5	
(Rodrigo and Rodrigo 1999) SR Grade 1+	IV steroid V po steroid[1] High/mod dose steroid V Low dose steroid[2]	Inclusion: Age > 18 yrs RCT English language	157[1] 369[2]		Effect size	95%CI			• Mean age 32 • Hydrocortisone equiv range (mg/kg/day) 4.2-83.3. Low dose < 13 mg/kg/day • Study identification inadequate – limited databases, English language only, no attempt to identify unpublished data. • Study quality assessed using an instrument that did not consider blinding or use of ITT analysis.
				Pulm fn (favouring po over IV treatment)	-0.14	-0.8, 0.31			
				Pulm fn (favouring medium and high doses over low dose steroid)	0.12	-0.18, 0.32			
(Nana et al. 1998a) RCT Grade 1- Country: Thailand	Budesonide inh 1600 µg bd V Prednisolone po starting 40 mg then daily 30, 25, 20, 15, 10, 5 mg. 1 week	Inclusion: Age 16-50 yrs FEV_1 20-50%PV on acute presentation	81		BDP	Pred	*P* value		• Mean age 38 and female 63% • Mean FEV_1 64%PV • FEV_1 %PV lower in budesonide group • ITT analysis not used since treatment withdrawals (4%) were not analysed • Study power not stated • Pharmaceutical company funded and supported trial
				% Δ FEV_1	17.3	17.6	*n.s.*		

Table 24. Summary of studies investigating the effect of pharmaceuticals (steroids) in acute asthma *(continued)*

Study source, design and evidence grading	Intervention Comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(FitzGerald et al. 2000) RCT Grade 1+ Country: Canada	Budesonide inh 600 µg Qid V Prednisone po 40 mg mane 7-10 days	Inclusion: Age 15-70 yrs FEV_1 > 50%PV post bronchodilator Discharged from ED Exclusion: Pharmaceutical limitations	185		BDP	Pred	95%CI (Diff)	• Mean age 28 and female 57% • Mean FEV_1 75%PV • Budesonide producer funded and supported trial • Despite authors claiming therapeutic equivalence the 95%CI was not entirely within the preset ± 10% criteria for relapse
				Relapse rate (%)	10	14	-7.5, 11	
				FEV_1 (L)	3.06	3.00	*n.s.*	

Theophylline

Chronic asthma

Table 25: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus theophylline) in chronic asthma

Study source, design and evidence grading	Intervention Comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Pollard et al. 1997) RCT Grade 1+ Country: United States	Salmeterol mdi (42 µg bd) V Theophylline po (Individual dose titrated slo-bd) V Placebo Inh and po 12 weeks	Inclusion: Age 12+ yrs FEV_1 > 50%PV 15+% increase in FEV_1 with salbutamol inh Exclusion: Other bronchodilators	484	12 weeks Mean change AM PEFR(cf. baseline) (L/min) Mean change (cf. baseline) Nighttime awakenings/wk Asthma symptom score Salbutamol use puffs/day Drug related adverse event	SLM +10.3 -0.7 -0.11 -1.1 9%	THP -4.5 -0.1 0.01 0.06 19%	*P* value *P*≤.02 *P*<.02 *P*<.02 *P*<.02 *P*<.05	• Mean age 31 and female 52% in salmeterol group; mean age 30 and 54% in theophylline group • 54% patients on concurrent ICS therapy • Pharmaceutical company funded and supported trial • Combined results of two identical trials

Table 25: Summary of studies investigating the effect of pharmaceuticals (long-acting β-agonists versus theophylline) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention Comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Nutini et al. 1998) RCT Grade 1- Country: Italy	Salmeterol inh 50 µg bd V Theophylline po 50 dose titrated bd 12 weeks (drug efficacy) 52 weeks (drug safety)	Inclusion: Age 18+ yrs FEV_1 50-80%PV 15+% increase in FEV_1 with 200 µg salbutamol inh Exclusion: Variable smoking history Asthma requiring emergency care – past month	112	12 weeks Symptom free Days Nights Days with no rescue medication use Days Nights QOL index score Adverse drug events	SLM 65.7% 65.7% 68.7% 70.1% 9.7 9	THP 56.8% 60.2% 57.2% 63.0% 8.6 18	*P* value *P*<.005 *P*<.01 *P*<.001 *P*<.001 N/A N/A	NNT 11 18 9 14	• Mean age 46 and female 44%, mean FEV_1 (L) 2.21 in SLM group; mean age 48 and 32% and mean FEV_1 (L) 2.10 in THP group • Pharmaceutical company funded and supported trial • Open study design • Intention to treat analysis

Table 26: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus theophylline) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Reed et al. 1998) RCT Grade 1+ Country: United States	Beclomethasone inh 84 µg Qid V Theophylline 1 year	Inclusion: Age 6-65 yrs FEV_1 >50%PV Exclusion: >5 pack years tobacco smoking Resp infection in past 3 weeks Pharmaceutical limitations	747		BEC	THP	*P* value	NNT	• Female 51% • 45% previously taken theophylline, 4% beclomethasone • 75% study completion rate • Theophylline dose determined by response • Study supported by phamaceutical company producing beclomethasone • No baseline data on mean age in two study groups • [1]For any day in the 12th month. There were significant differences in earlier months that favoured beclomethasone.
				Moderately severe or worse symptoms[1]	25.8%	30.5%	*n.s.*		
				Systemic steroid use over course of study	20%	29%	*P* = .009	11	
(Ukena et al. 1997) RCT Grade 1+ Country: Germany, Hungary, Austria	Beclomethasone inh 200 µg bd + Theophylline V Beclomethasone inh 400 µg bd 6 weeks	Inclusion: Age 18-70 years FEV_1 50-85%PV Asthma not controlled on beclomethasone 400 µg daily or equivalent Exclusion: Severe asthma attack or lower resp infection within 1 month Current smoker Pharmaceutical limitations	133		Combined	BEC	*P* value		• Median age 48 and female 44% • FEV_1 75%PV • Data not presented but no significant difference in rescue med use between groups • ITT analysis not presented in paper but results similar to per protocol analysis presented • Producers of theophylline funded and supported trial
				Δ FEV_1 (L)	0.26	0.19	*n.s.*		

Table 26: Summary of studies investigating the effect of pharmaceuticals (inhaled steroids versus theophylline) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Evans et al. 1997) RCT Grade 1+ Country: United Kingdom and Sweden	Budesonide inh 400 µg bd + theophylline po 250 mg (if < 80 kg) or 375 mg (if ≥ 80 kg) bd V Budesonide inh 800 µg bd 3 months	Inclusion: FEV_1 > 50%PV Exclusion: Pharmaceutical limitations Asthma exacerbation within 3 weeks of run in	62		THP + BDP	BDP	*P* value	• Mean age 39 and female 60% • Mean FEV_1 75%PV • Supported by pharmaceutical company that produces theophylline
				Improvement in FEV_1 (L)	0.21	0.11	*P* = 0.03	
				Improvement in FVC (L)	0.26	0.18	*P* = 0.03	
				Day time symptom scores	N/A	N/A	*P* = 0.26	
				Night time symptom scores	N/A	N/A	*P* = 0.59	
				Daytime rescue med use	N/A	N/A	*P* = 0.57	
				Nighttime rescue med use	N/A	N/A	*P* = 0.97	

Inhaler devices

Chronic asthma

Table 27: Summary of studies investigating inhaler devices in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Nelson et al. 1999) RCT Grade 1+ Country: United States	Salbutamol dry powder inh 216 µg Qid V Salbutamol mdi 180 µg Qid V Placebo 12 weeks	Inclusion: Age ≥ 12 yrs Nonsmoker Exclusion: No changes in current asthma meds, no hospital admissions or ED visits for asthma within 4 weeks	283	FEV_1 (L)	DPI 2.27	mdi 2.43	*P* value *n.s.*	• Mean age 34 and female 55% • Mean FEV_1 64%PV • Text stated no significant difference in asthma exacerbation, use of rescue med and symptom score (Specific data not provided) • Unclear whether ITT analysis was used • Study power not defined • Grant provided by the producers of the dry powder inhaler
(Seppala et al. 1998) CO Grade 1+ Country: Germany	Salbutamol dry powder inh (Taifun™) V Salbutamol mdi + spacer Single dose each	Inclusion: Age 20-69 yrs FEV_1 35-70%PV Exclusion: Pharmaceutical limitations	36	Δ FEV_1 (%)	DPI 47.2	mdi 44.7	90%CI (DPI, mdi ratio) 95%, 120%	• Mean age 44 and female 41% • Mean FEV_1 58%PV • Results reported on 90% of randomised population • No data on equivalence at baseline • Pharmaceutical company involved at authorship level

Table 27: Summary of studies investigating inhaler devices in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Geoffroy et al. 1999) CO Grade 1- Country: United States	Salbutamol Spiros™ dry inh 180 µg Qid V Spiros™ dry inh 90 µg Qid V mdi 180 µg Qid V mdi 90 µg Qid V Placebo 1 day each	Inclusion: Age 18-65 yrs FEV_1 40-70%PV Within ± 20% ideal body weight Exclusion: Use of tobacco products within 6 months	60		mdi 180	DPI 180	mdi 90	DPI 80	• Mean age 30 and female 45% • No significant differences between treatment results presented • 73% of randomised population included in analysis • Pharmaceutical company producing Spiros™ inhaler funded and supported trial • No baseline comparison data presented post-randomisation • Power of study not clear
				FEV_1 max (L)	2.91	2.92	2.82	2.82	
				Time to $FEV_1 \geq 15\%$ baseline (min)	47.6	56.1	59.6	38.1	
				Duration when $FEV_1 \geq 15\%$ baseline (min)	234.6	221.2	174.9	212.4	

Table 27. Summary of studies investigating inhaler devices in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Lofdahl et al. 1997) CO Grade 1- Country: Sweden	Salbutamol turbuhaler (TBH) 200 µg daily V Salbutamol turbuhaler (TBH) 50 µg daily V Salbutamol mdi 400 µg daily V Salbutamol mdi 100 µg daily V Placebo Single dose each	Inclusion: Age 18-70 yrs $FEV_1 \geq 35\%PV$	50	FEV_1 ratio %	TBH50/mdi 100 102.0	TBH200/mdi 400 99.0	TBH200/TBH50 102.8	mdi400/mdi100 105.9	• Mean age 46 and female 46% • Mean FEV_1 65%PV • No baseline data post-randomisation • Pharmaceutical company involvement at authorship level • Study power not documented
				95%CI	99.7, 104.3	96.8, 101.3	100.5, 105.2	103.6, 108.3	

Table 27: Summary of studies investigating inhaler devices in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Vink-van Wijngaarden et al. 1998) RCT Grade 1+ Country: Netherlands	Beclomethasone rotahaler 400 µg bd V Beclomethasone cyclohaler 400 µg bd 16 weeks	Inclusion: Age 18-60 yrs FEV_1 > 50%PV Stabilised on 800 µg BEC daily for at least 6 months Exclusion: Resp infection within 6 weeks Asthma exacerbation within 2 months Pharmaceutical limitations	182		Diff (CYC – ROT)	90%CI		• Mean age 41 and female 41% • Mean FEV_1 82%PV • No significant difference in rescue med use or symp score (Specific data not provided) • Unclear if ITT analysis was used
				AM PEFR (L/min)	5	-20, 31		
(Galant et al. 1999) RCT Grade 1+ Country: United States	Fluticasone inh 500 µg bd Diskus V Diskhaler V Placebo 12 weeks	Inclusion: Age ≥ 12 yrs FEV_1 50-80%PV Exclusion: PO or parenteral steroids within 4 weeks of the study	229		DU	DH	*P* value	• Mean age 33 and female 45% • Mean FEV_1 67%PV • Data excluded from two sites since it didn't meet quality standards • Power to detect a difference in FEV_1 of 0.25 L < 80% due to withdrawal of the 2 study sites. Inadequate power to comment on equivalence. • Pharmaceutical company funded and supported trial.
				Δ AM FEV_1 (L)	0.52	0.40	*n.s.*	
				Δ salbutamol use (puffs/day)	-1.54	-1.41	*n.s.*	
				Δ night awakenings (n/week)	-0.03	0.00	*n.s.*	
				Δ symptom score	-0.20	-0.10	*n.s.*	

Table 27. Summary of studies investigating inhaler devices in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Pieters et al. 1998) RCT Grade 1- Country: Netherlands	Fluticasone 250 µg bd Diskus/ Accuhaler (D/A) V Diskhaler (DH) 12 weeks	Inclusion: Age 18-79 yrs FEV_1 50-90%PV Required between 400 and 1000 µg steroid per day at study start Exclusion: Pharmaceutical limitations	364		D/A	DH	*P* value	• Mean age 49 and female 43% • Mean FEV_1 69%PV • ITT not used since noncompliant patients were not included in analysis • Pharmaceutical company producing both interventions involved at authorship level • Study power not stated
				Δ AM PEFR (L/min)	19	20	*n.s.*	
				Median symptom score	0	0	*n.s.*	
				Median % rescue free days	63	60	*n.s.*	
				Median % rescue free nights	93	96	*n.s.*	
(Wolfe et al. 2000) RCT Grade 1+ Country: United States	Salmeterol diskus 50 µg bd V Salmeterol mdi 42 µg bd V Placebo 12 weeks	Inclusion: Age ≥ 12 yrs FEV_1 50-85%PV Less than 10 pack-years tobacco use and non smoker for 1 year and not exposed to secondary smoke for ≥ 4 hours/day Exclusion: Resp or middle ear infection within 6 weeks of entry	498		mdi	DU	*P* value	• Mean age 34 and female 53% • Mean FEV_1 68%PV • Pharmaceutical company funded and supported trial • Statistical power not stipulated so unable to assess equivalence
				Δ days without rescue med use (%)	29	23	*n.s.*	
				Δ nights without awakening (%)	16	12	*n.s.*	
				Δ days without symptoms (%)	20	19	*n.s.*	

Acute asthma

Table 28: Summary of studies investigating inhaler devices in acute asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Nana et al. 1998b) RCT Grade 1+ Country: Thailand	Salbutamol turbuhaler V mdi (turbuhaler doses half mdi doses. Eight doses over 90 mins)	Inclusion: Age 16-50 yrs FEV_1 20-50%PV Attending ED	86		TBH	mdi	*P* value	• Mean age 38 and female 63% • Mean FEV_1 37%PV • Pharmaceutical company involved in all study aspects • Primary endpoint was measured at half way point in the dosing schedule • 80% power to detect a difference in the increase in FEV_1 that was at least 62% of the standard deviation at the 5% significance level
				Δ FEV_1 at 55 mins (L)	0.47	0.46	*n.s.*	
				Symptom score	8	6	*n.s.*	

Propellants

Chronic asthma

Table 29: Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Gross et al. 1999) RCT Grade 1+ Country: United States	Beclomethasone HFA inh 400 µg daily V Beclomethasone CFC inh 400 µg daily V Placebo 12 weeks	Inclusion: Age ≥ 12 yrs FEV_1 ≥ 60%PV Exclusion: Current or recent smoker History of life threatening asthma Pharmaceutical limitations	347	Δ AM PEFR (l/min)	HFA -5.3	CFC -14.0	*P* value *n.s.*	• Mean age 34 and female 53% • Mean FEV_1 67%PV • PO steroid given for 7-12 days before randomisation • Symptom score, rescue medication use and Δ AM PEFR defined as equivalent outcome between propellants. • Partial concealment only with H and corresponding placebo requiring half the puffs of CFC a its corresponding placebo – potential bias based on compliance • Pharmaceutical company func and supported trial
(Juniper and Buist 1999) RCT Grade 1+ Country: United States	Beclomethasone HFA inh 400 µg daily V Beclomethasone CFC inh 400 µg daily V Placebo 12 weeks	Inclusion: Age ≥ 12 yrs FEV_1 ≥ 60%PV Exclusion: Current or recent smoker History of life threatening asthma Pharmaceutical limitations	347	Asthma Quality of life: Overall Activity limitations Symptoms Emotions Environment	HFA 5.66 5.86 5.50 5.62 5.62	CFC 5.55 5.70 5.44 5.52 5.51	*P* value *n.s.* *n.s.* *n.s.* *n.s.* *n.s.*	• Same study as (Gross et al. 199 and same limitations • No assessment of equivalence made

Table 29: Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Dahl et al. 1997) CO Grade 1+ Country: Denmark, Norway	Beclomethasone 200-600 µg daily HFA V CFC 4 weeks each	Inclusion: Age ≥ 18 yrs FEV_1 ≥ 40%PV Currently taking ≤ 600 µg daily beclomethasone Exclusion: Upper resp infection within 2 weeks and lower resp infection within 4 weeks	68		HFA	CFC	90%CI for HFA	Equiv level	• Mean age 49 • pm results were similar to the a results presented (all met equivalence criteria) • No baseline data post-randomisation presented • Equivalence criteria were libera • Pharmaceutical company func and supported trial
				FEV_1 (L)	2.9	3.0	-0.06, 0.04	-0.44, 0.44	
				AM wheeze	0.4	0.4	-0.06, 0.02	-0.2, 0.2	
				AM SOB	0.4	0.4	-0.05, 0.05	-0.2, 0.2	
				AM cough	0.5	0.5	-0.12, 0.01	-0.2, 0.2	
				Sleep disturbance	0.6	0.7	-0.13, 0.02	-0.2, 0.2	
				AM rescue med use	0.8	0.8	-0.18, 0.10	-0.2, 0.2	
(Milanowski et al. 1999) RCT Grade 1+ Country: United Kingdom, Ireland, Poland	Beclomethasone inh 100 µg Qid HFA V CFC 6 weeks	Inclusion: Age >12 years FEV_1 50-80%PV post bronchodilator Exclusion: Recent hospitalisation for asthma exacerbation Recent therapy for URTI	119		HFA	CFC	90%CI diff		• Mean age 39 and female 44% • Mean FEV_1 67%PV • 90% power to detect a differen in FEV_1 between groups of >0.2 = 0.05) • Pharmaceutical company func and supported trial
				FEV_1 (L)	2.6	2.5	-0.14, 0.35		
							P value		
				Proportion patients with cough (%)	29.8	45.8	*P* = 0.11		
				Proportion patients with wheeze (%)	36.2	39.6	*P* = 0.73		
				Any adverse event (%)	58	60	*n.s.*		
(Milanowski et al. 1999) RCT Grade 1+ Country: United Kingdom, Ireland, Poland	Beclomethasone inh 500 µg Qid HFA V CFC 12 weeks	Inclusion: Age >12 years FEV_1 50-80%PV post bronchodilator Taking 800-2000 µg daily BEC-CFC Exclusion: Recent hospitalisation for asthma exacerbation Recent therapy for URTI	119		HFA	CFC	90%CI diff		• Mean age 44 and female 55% • Mean FEV_1 70%PV • 90% power to detect a differen in FEV_1 between groups of >0.2 5% significance level • Same study as above
				FEV_1 (L)	2.3	2.4	-0.34, 0.5		
							P value		
				Proportion patients with cough (%)	36.2	48.9	*P* = 0.21		
				Proportion patients with wheeze (%)	40.4	46.8	*P* = 0.53		
				Any adverse event (%)	73	86	*n.s.*		

Table 29: Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Harrison et al. 1999) RCT Grade 1- Country: United States	Beclomethasone inh HFA 800, 400, 200 µg daily V CFC 800 µg daily V Placebo 2 weeks	Inclusion: $FEV_1 \geq 60\%PV$ No systemic steroids in past 3 months Non-smoker	43		HFA800	CFC800	*P* value		• No demographic details provid • No baseline comparison • Producers of HFA preparation funded and supported trial • Statistical comparison betweer HFA and CFC preparations limit to the 800 µg dose
				% Δ 24 hour urinary free cortisol	-37.3	-47.4	*n.s.*		
(Davies et al. 1998) RCT Grade 1+ Country: United Kingdom	Beclomethasone HFA 800 µg daily V Beclomethasone CFC 1500 µg daily 12 weeks	Inclusion: Age 18-65 years PEFR 50-85%PV Inadequate control on 400-800 µg daily inh steroid Exclusion: Resp infection within 4 weeks of study start	233		HFA	CFC	*P* value for equivalence		• Mean age 40 andmale 56% • Mean FEV_1 66%PV • Producer of the HFA preparatic funded and supported trial • 89% of study participants randomised were analysed
				Δ PEFR (L/min)	-22.3	-21.9	$P < .001$		
					Mean diff (HFA and CFC)	90%CI			
				Wheeze	0.05	-0.12, 0.22			
				Cough	0.04	-0.15, 0.23			
				SOB	-0.05	-0.24, 0.13			
				Chest tightness	-0.00	-0.19, 0.18			
(Tonnel et al. 2000) RCT Grade 1+ Country: France	Fluticasone inh 250 µg bd HFA V CFC 4 weeks	Inclusion: Age ≥ 18 yrs FEV_1 50-90%PV Required 400-1000 µg daily beclomethasone or equivalent Exclusion: Required antibiotics, hospitalised or received po/parenteral steroids in 4 weeks preceding study	380		HFA	CFC	Adj diff	90%CI	• Mean age 43 and female 49% • Funded by pharmaceutical company producing fluticason • [1]Met criteria for therapeutic equivalence • Method of randomisation uncle
				Adjusted mean AM PEFR	399	400	-1	-7,5[1]	
				Median days with no rescue med. use (%)	83	83			
				Adverse events (%)	26	27			

Table 29: Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Perruchoud et al. 2000) RCT Grade 1+ Country: 4 countries	Fluticasone inh 500 µg bd HFA V CFC 12 months	Inclusion: Age ≥ 16 yrs FEV_1 50-90%PV Required 1-2 mg daily beclomethasone or equivalent Exclusion: Required antibiotics for resp infection, or change in regular asthma medication in 4 weeks preceding study PO/parenteral steroids ≥ 2 times in previous 4 months	412		HFA	CFC	Adj diff	90%CI	• Mean age 47 and female 52% • Imbalance in gender distributio baseline • Funded by pharmaceutical company producing fluticason • [1]Met criteria for therapeutic equivalence
				Adjusted mean Δ AM FEV_1	0.18	0.11	0.07	0.00, 0.14[1]	
				Median symp score	0	0			
				Adverse events (%)	82	78			
				Serum cortisol (12 mth/baseline ratio)	0.96	0.96		0.89, 1.12	
(Ayres et al. 2000) CO Grade 1+ Country: United Kingdom	Fluticasone inh 1 mg bd HFA V CFC 6 weeks each	Inclusion: Age > 16 yrs FEV_1 ≤ 90%PV at randomisation Required 2-4 mg daily of beclomethasone or budesonide or ≤1 mg daily fluticasone Exclusion: Current smoker or smoked within previous 6 weeks Change in regular asthma meds, required antibiotics, hospitalised for resp disease or received po steroids (<10 mg daily) in 4 weeks preceding study	119		HFA	CFC	90%CI		• Mean age 49 and female 57% • No washout period • Difference in mean PEFR at baseline between sequence or • Funded by producers of fluticasone • [1]Met criteria for therapeutic equivalence
				Δ am PEFR (L/min)	2	0	-7,6[1]		
				Median % symp free nights	89	86	*n.s.*		
				Median days no additional bronchodilator	10	4	*n.s.*		
				Median nights no additional bronchodilator	82	82	*n.s.*		
				% patients reporting an adverse event	77	75	*n.s.*		

Table 29: Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes					Comments
(Welch et al. 1999) RCT Grade 1+ Country: United States	Triamcinolone HFA V CFC V Placebo Doses 150, 300, 600 µg daily for HFA and CFC 8 weeks	Inclusion: Age ≥ 18 yrs FEV_1 50-80%PV at randomisation Exclusion: Current smoker or past history of ≥ 10 pack-years tobacco History of life threatening asthma Upper resp infection within 30 days	514		Δ AM PEFR	Δ symptom score	Δ nights awake		• Mean age 39 and female 61% • Mean FEV_1 65%PV • Pharmaceutical company func and supported trial • 90% power to detect 10% difference in FEV_1 (compared v placebo)
				HFA150	9.2	-1.52	-0.27		
				HFA300	36.4	-2.03	-0.58		
				HFA600	44.9	-2.57	-0.75		
				CFC150	24.3	-1.27	-0.37		
				CFC300	23.4	-2.01	-0.43		
				CFC600	33.7	-2.34	-0.57		
					n.s. but not equivalent	*n.s.* but not equivalent	Therapeutic equivalence		
(Jacobson et al. 1999) RCT Grade 1+ Country: United States	Triamcinolone HFA 450, 900, 1800 µg daily V Triamcinolone CFC 450, 900 µg daily V Placebo 12 weeks	Inclusion: Age ≥ 18 yrs FEV_1 40-80%PV Exclusion: History of life threatening asthma Recent hospitalisation for asthma exacerbation Upper resp infection	538		HFA450	HFA900	CFC450	CFC900	• Mean age 40 • Mean FEV_1 61%PV • All presented results had non-significant differences betweer CFC and HFA propellant (whicl extended to HFA1800 µg dose) • Pharmaceutical company func and supported trial • [1]Therapeutic equivalence
				% Δ FEV_1	22.2	23.1	11.5	18.4	
				Symp score	-1.7	-2.0	-2.0	-1.9	
				Night awakening (n/night)[1]	-0.4	-0.5	-0.4	-0.6	
				Any adverse event (%)	65.3	71.1	69.4	66.7	

Table 29: Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Baumgarten et al. 2000) RCT Grade 1+ Country: Germany	Salbutamol inh 100 µg PRN HFA V CFC 4 weeks	Inclusion: Age ≥ 18 yrs FEV_1 50-100%PV Average of at least 1 actuation per day and not more than 12 actuations over 2 days in the last 7 days of run-in Exclusion: Changes in regular asthma medication or a deterioration in or exacerbation of asthma 4 weeks prior to start of run-in phase Pharmaceutical limitations	423		HFA	CFC	*P* value	• Mean age 48 and female 49% • Patient maintained on usual regular treatment • Some FEV_1 /PEFR measurement may have been bronchodilato influenced • Pharmaceutical company fund and supported trial
				Median salbutamol use (puffs/4 weeks)	110	111	*n.s.*	
				Median symp score	1	1	*n.s.*	
				Adverse e vents	26	19	*n.s.*	
							90%CI	
				Adjusted Δ am PEFR (L/min)	5	4	-4,6	
				Asthma exacerbation (%)	4	5	0,0	
(Bleecker et al. 1998) RCT Grade 1+ Country: United States	Salbutamol HFA 180 µg Qid V Salbutamol CFC 180 µg Qid V Placebo 12 weeks	Inclusion: Age 18-65 years FEV_1 40-80%PV Able to withhold inh bronchodilators for ≥ 8 hours Exclusion: Recent resp infection Oral steroid use within 4 weeks of study start Smoking history within 2 years	565		HFA	CFC	90%CI diff	• Mean age 36 and female 59% • Pharmaceutical producer of HF preparation funded and supported trial • [1]Met criteria for equivalence • Responder if FEV_1 exceeeded baseline by at least 15% within minutes post dose at that visit
				Responders (%)	73	74	-0.07, 0.07[1]	

Table 29. Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Tinkelman et al. 1998) RCT Grade 1+ Country: United States	Salbutamol HFA 180 µg Qid V Salbutamol CFC 180 µg Qid V Placebo 12 weeks	Inclusion: Age 18-65 years FEV_1 40-80%PV Able to withhold inh bronchodilators for ≥ 8 hours Exclusion: Recent resp infection Oral steroid use within 4 weeks of study start Smoking history within 2 years	565	Increased asthma symptoms within 15 mins of drug use (%)	HFA 2	CFC 2	*P* value *n.s.*	• Same study as (Bleecker et al. 1998) • Mean age 36 and female 59% • Pharmaceutical producer of HF preparation funded and supported trial
(Furukawa et al. 1999) RCT Grade 1+ Country: United States	Cromolyn Sodium HFA inh 2 mg Qid V Cromolyn Sodium CFC inh 2 mg Qid V Placebo 12 weeks	Inclusion: Age ≥ 12 yrs FEV_1 ≥ 60%PV Exclusion: Current or recent smoker History of life threatening asthma Pharmaceutical limitations	280	Δ symptom score n (%) Δ PEFR (l/min) Δ rescue med use (%) FEV_1 (L) Physician rated the intervention as moderately or very effective (%) Patient rated the intervention as moderately or very effective (%) Adverse event reported (%)	CFC 0.63 (-22) 5.7 -13 3.00 63 73 74	HFA 0.83 (-22) 21.9 -27 2.80 56 77 76	*P* value *n.s.* *n.s.* *n.s.* *n.s.* *P* = .04 *n.s.* *n.s.*	• Mean age 29 and female 55% • FEV_1 74%PV • Study had 90% power to detec difference in the symptom scor 0.3 at the 5% significance level • Producers of HFA preparation funded and supported trial

Table 29. Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Blumenthal et al. 1998) RCT Grade 1+ Country: United States	Cromolyn sodium inh 2 mg Qid HFA V CFC V Placebo 12 weeks	Inclusion: Age ≥ 12 years FEV_1 50-90%PV Exclusion: Current or recent smoker History of life threatening asthma exacerbations Pharmaceutical limitations	366		HFA	CFC	*P* value	• Mean age 31 and female 53% • Mean FEV_1 75%PV • 90% power to detect a 0.3 poir difference in symptom score (5 significance level) • Pharmaceutical company func and supported trial
				FEV_1 (L)	2.95	2.80	*n.s.*	
				Δ symp score	-0.71	-0.74	*n.s.*	
				Δ rescue med use (%)	-33%	-38%	*n.s.*	

Table 29: Summary of studies investigating the effect of pharmaceuticals (CFC V HFA propellant) in chronic asthma *(continued)*

Study source, design and evidence grading	Intervention comparison and study duration	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Goldberg et al. 2000) RCT Grade 1+ Country: Germany	Fenoterol inh 200 µg Qid HFA V CFC 12 weeks	Inclusion: Age 18-65 yrs FEV_1 40-80%PV Current non-smoker with a history of ≤ 10 pack-years Exclusion: Upper resp infection, or hospitalisation due to exacerbation of asthma 4 weeks prior to start of run-in phase Pharmaceutical limitations	290		HFA	CFC	*P* value	• Mean age 41 and female 46% • Mean FEV_1 62%PV • Pharmaceutical company func and supported trial • 81% of randomised population analysed at endpoint
				Adverse events (%)	29.9	28.0	*n.s.*	
				FEV_1 (L)	2.2	2.1	*n.s.*	
(Bronsky et al. 1999) RCT Grade 1- Country: United States	Salbutamol inh 2 puffs bd + PRN CFC V HFA 12 weeks	Inclusion: Age 18-65 yrs FEV_1 40-80%PV 12 month history of asthma requiring β-agonist for symptom relief	51		CFC	HFA	*P* value	• Mean age 37 years and female 57% • Mean FEV_1 61%PV • No information on blinding, stu power or ITT analysis • Salbutamol dosage not stated • Pharmaceutical company func and supported trial
				Peak % Δ from predose FEV_1	35.8	36.1	*n.s.*	
				Adverse events (%)	88	100	*n.s.*	
				Δ pulse			*n.s.*	
				Δ BP			*n.s.*	

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Appendix 1

SEARCH STRATEGIES FOR ASTHMA THERAPEUTICS

Medline One

1 exp asthma/dt (2876)
2 randomized controlled trials/ or randomized controlled trial.pt. (44090)
3 controlled clinical trials/ or controlled clinical trial.pt. (9382)
4 2 or 3 (53209)
5 1 and 4 (798)
6 (child: or pediatric: or paediatric:).ti. (43867)
7 5 not 6 (643)
8 (letter or review of reported cases).pt. (96620)
9 news.pt. (14510)
10 case report/ (143192)
11 or/8-10 (227583)
12 7 not 11 (631)
13 meta-analysis/ or meta-analysis.pt. (3589)
14 guidelines/ or practice guidelines/ or guideline.pt. (12819)
15 13 or 14 (16300)
16 1 and 15 (142)
17 (systematic: adj (review or overview)).mp. (1121)
18 1 and 17 (8)
19 16 or 18 (147)
20 12 not 19 (613)
21 from 20 keep 1-200 (200)
22 from 20 keep 201-400 (200)
23 from 20 keep 401-600 (200)
24 from 20 keep 601-613 (13)
25 exp anti-asthmatic agents/ (22855)
26 exp Anti-Asthmatic Agents/ad, ae, ct, tu (6097)
27 4 and 26 (1536)
28 exp asthma/ (9422)
29 27 and 28 (698)
30 limit 29 to human (697)
31 30 not 11 (687)
32 31 not 12 (181)
33 from 32 keep 1-181 (181)
34 Bronchodilator Agents/ad, ae, po, ct, tu, to (1504)
35 28 and 34 (814)
36 35 and 4 (321)
37 36 not 11 (319)
38 limit 37 to human (319)
39 38 not 20 (93)
40 39 or 33 (189)
41 from 40 keep 1-189 (189)
42 26 or 34 (6110)
43 13 or 14 or 17 (17031)
44 42 and 43 (179)
45 19 or 20 or 41 (939)
46 44 not 45 (77)
47 from 46 keep 1-77 (77)

Medline Two

1 exp ASTHMA/ci, nu, dh, dt, px, rt, rh, su, th (4549)
2 limit 1 to (clinical trial or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) (1051)
3 child:.ti. (36346)
4 2 not 3 (856)
5 animal/ (437966)
6 human/ (1090130)
7 5 and 6 (137484)
8 4 and (6 or 7) (855)
9 research/ (7508)
10 Clinical Protocols/ (1880)
11 feasibility studies/ (3750)
12 reproducibility of results/ (27183)
13 research design/ (5737)
14 double-blind method/ (13842)
15 patient selection/ (5489)
16 random allocation/ (5354)
17 sample size/ (703)
18 or/9-17 (68066)
19 epidemiologic research design/ (185)
20 crossover studies/ (4948)
21 matched pair analysis/ (540)
22 sample size/ (703)
23 sensitivity.mp. and "specificity"/ (12423)
24 Single-Blind Method/ (2297)
25 or/19-24 (20555)
26 clinical trials/ (9996)
27 Clinical Trials, Phase IV/ (20)
28 controlled clinical trials/ (855)
29 multicenter trials/ (1496)
30 randomized controlled trials/ (7360)
31 or/26-30 (18323)
32 placebos/ (2285)
33 comparative study/ (148426)
34 "Outcome Assessment (Health Care)"/ (5040)
35 treatment outcome/ (55175)
36 medical futility/ (300)
37 treatment failure/ (3137)
38 or/32-37 (201054)
39 random:.mp. (67238)
40 single-blind:.mp. (2622)
41 double-blind:.mp. (15487)
42 triple-blind:.mp. (17)
43 double-dummy:.mp. (217)
44 mask:.mp. (5078)
45 sham.mp. (5564)
46 placebo:.mp. (15900)
47 control: trial:.mp. (7404)
48 efficacy.mp. (40563)
49 effectiveness.mp. (19336)
50 or/39-49 (129476)
51 8 and 25 and 38 (110)
52 8 and (25 or 31 or 38 or 50) (748)
53 52 not 51 (638)
54 8 and 18 (450)
55 8 and 25 (218)
56 8 and 31 (14)
57 8 and 38 (420)

58 8 and 50 (685)
59 55 not 54 (52)
60 56 not 55 (14)
61 from 54 keep (SELECTED REFERENCES)

Embase

1 exp ASTHMA/pc, rt, dm, rh, dt, su, th (15382)
2 Major Clinical Study/ (503543)
3 Clinical Study/ (1085)
4 Clinical Article/ (546908)
5 Controlled Study/ (1080347)
6 PREVENTION/ (9035)
7 THERAPY/ (9171)
8 or/2-7 (1794449)
9 1 and 8 (6810)
10 limit 9 to yr=1997-2001 (2459)
11 (child: or pediatric: or infant:).ti. (141191)
12 10 not 11 (1985)
13 animal/ (6599)
14 human/ (2803280)
15 13 and 14 (1153)
16 12 and (14 or 15) (1897)
17 Controlled Study/ (1080347)
18 Case Control Study/ (5166)
19 randomized controlled trial/ (49059)
20 or/17-19 (1085585)
21 drug comparison/ (1788)
22 Clinical Trial/ (184432)
23 multicenter study/ (17496)
24 Phase 4 Clinical Trial/ (251)
25 or/21-24 (186669)
26 Major Clinical Study/ (503543)
27 medical research/ (20276)
28 clinical research/ (6842)
29 drug research/ (6605)
30 or/27-29 (32559)
31 Evidence Based Medicine/ (3327)
32 meta-analysis/ (10677)
33 outcomes research/ (7617)
34 or/31-33 (20997)
35 RANDOMIZATION/ (2624)
36 crossover procedure/ (10029)
37 double blind procedure/ (32575)
38 single blind procedure/ (2880)
39 placebo/ (24698)
40 or/35-39 (55833)
41 triple-blind.mp. (42)
42 double-dummy.mp. (646)
43 mask:.mp. (14340)
44 sham.mp. (15088)
45 placebo:.mp. (56007)
46 control: trial:.mp. (59723)
47 efficacy.mp. (186786)
48 effectiveness.mp. (62386)
49 or/41-48 (324858)
50 16 and (20 or 21 or 25 or 26 or 30 or 34 or 40 or 49) (1723)
51 limit 50 to yr=1997-2001 (1723)
52 16 and (20 or 21 or 25 or 26 or 30 or 34 or 40) (1669)

53 limit 52 to yr=1997-2001 (1669)
54 16 and 20 (1229)
55 16 and 21 (0)
56 16 and 25 (986)
57 16 and 26 (881)
58 16 and 30 (4)
59 16 and 34 (69)
60 16 and 40 (669)
61 16 and 49 (1010)
62 or/54-61 (1723)
63 exp asthma/dt (13531)
64 63 and 8 (6057)
65 64 not 11 (4972)
66 65 and (14 or 15) (4807)
67 66 and (20 or 21 or 25 of 26.mp. or 30 or 34 or 40 or 49) (3437)
68 limit 67 to yr=1997-2001 (1313)
69 from 51 keep (SELECTED REFERENCES)

Embase Two

1 exp ASTHMA/pc, rt, dm, rh, dt, su, th (15382)
2 randomized controlled trial/ (49059)
3 Evidence Based Medicine/ (3327)
4 meta-analysis/ (10677)
5 RANDOMIZATION/ (2624)
6 double blind procedure/ (32575)
7 single blind procedure/ (2880)
8 placebo/ (24698)
9 triple-blind.mp. (42)
10 double-dummy.mp. (646)
11 mask:.mp. (14340)
12 sham.mp. (15088)
13 placebo:.mp. (56007)
14 control: trial:.mp. (59723)
15 controlled clinical trial.mp. (1824)
16 (systematic: adj review:).mp. (1701)
17 (systematic: adj overview).mp. (106)
18 practice guideline/ (21230)
19 or/2-18 (161913)
20 1 and 19 (3232)
21 limit 20 to yr=1997-2000 (1661)
22 (child: or toddler or infan:).ti. (127485)
23 adult:.ti. (43216)
24 22 and 23 (3236)
25 22 not 24 (124249)
26 21 not 25 (1421)
27 ((rhinitis or eczema) not asthma).ti. (2997)
28 26 not 27 (1418)
29 (healthy volunteer: or healthy subject: or human volunteer:).ti. (5584)
30 28 not 29 (1415)
31 from 30 keep (SELECTED REFERENCES)
32 from 30 keep (SELECTED REFERENCES)
33 from 32 keep (SELECTED REFERENCES)
34 from 30 keep (SELECTED REFERENCES)
35 from 34 keep (SELECTED REFERENCES)
36 31 or 33 or 35 (306)
37 from 30 keep (SELECTED REFERENCES)
38 37 not 36 (444)
39 (paediatric: or pediatric: or rhinitis or chronic obstructive or copd or child:).ti,ab. (221742)

40 (child: or paediatric: or pediatric:).jw. (105360)
41 38 and (39 or 40) (45)
42 from 41 keep (SELECTED REFERENCES)
43 38 not 42 (430)
44 from 43 keep (SELECTED REFERENCES)

Embase Three

1 randomized controlled trial/ (49243)
2 meta-analysis/ (10712)
3 RANDOMIZATION/ (2628)
4 double blind procedure/ (32653)
5 single blind procedure/ (2890)
6 placebo/ (24762)
7 triple-blind.mp. (42)
8 double-dummy.mp. (647)
9 mask:.mp. (14369)
10 sham.mp. (15119)
11 placebo:.mp. (56121)
12 control: trial:.mp. (59936)
13 controlled clinical trial.mp. (1827)
14 (systematic: adj review:).mp. (1712)
15 (systematic: adj overview).mp. (106)
16 practice guideline/ (21364)
17 or/1-16 (160253)
18 asthma/dt (12762)
19 17 and 18 (2792)
20 limit 19 to yr=1997-2000 (1443)
21 letter:.ti. (26037)
22 case report/ (430369)
23 letter/ (200255)
24 or/21-23 (590898)
25 20 not 24 (1395)
26 (paediatric: or pediatric: or child:).jw. (105679)
27 25 not 26 (1288)
28 ((paediatric: or pediatric: or child:) and adult:).ti. (3231)
29 (paediatric: or pediatric: or child:).ti. (119959)
30 29 not 28 (116728)
31 27 not 30 (1133)
32 ((rhinitis or copd or chronic obstructive) and asthma).ti. (526)
33 (chronic obstructive or copd or rhinitis).ti. (6131)
34 33 not 32 (5605)
35 31 not 34 (1116)
36 limit 35 to yr=2000 (221)
37 limit 35 to yr=1999 (318)
38 limit 35 to yr=1998 (300)
39 limit 35 to yr=1997 (278)
40 40 vfrom 36 keep (SELECTED REFERENCES)
41 41 from 37 keep (SELECTED REFERENCES)
42 42 from 38 keep (SELECTED REFERENCES)
43 43 from 39 keep (SELECTED REFERENCES)

Cinahl

1 exp ASTHMA/dt, th [Drug Therapy, Therapy] (1561)
2 Double-Blind Studies/ (1712)
3 Random Assignment/ (3234)
4 placebos/ (968)

5 random sample/ (4022)
6 simple random sample/ (151)
7 Stratified Random Sample/ (704)
8 systematic random sample/ (53)
9 random:.mp. (14963)
10 single-blind:.mp. (510)
11 double-blind:.mp. (2059)
12 triple-blind:.mp. (2)
13 double-dummy:.mp. (27)
14 mask:.mp. (737)
15 sham.mp. (203)
16 placebo:.mp. (2168)
17 (control: adj2 trial:).mp. (2586)
18 or/2-17 (17997)
19 1 and 18 (201)
20 limit 19 to yr=1997-2000 (145)
21 (child: or infant: or pediatric:).ti. (28390)
22 20 not 21 (120)
23 from 22 keep (SELECTED REFERENCES)

Current Contents

asthma.mp.
double blind:.ti,ab.
meta-analy:.ti,ab.
(systematic: adj (review or overview)).ti,ab.
randomized controlled trial:.ti,ab.
controlled clinical trial:.ti,ab.
or/2-6
1 and 7
limit 8 to yr=1997-2000
(child: or paediatric or pediatric).ti.
9 not 10
from 11 keep (SELECTED REFERENCES)
from 11 keep (SELECTED REFERENCES)
12 or 13
from 11 keep (SELECTED REFERENCES)
from 11 keep (SELECTED REFERENCES)
14 or 15 or 16
11 not 17
(child: or infan: or pediatric: or paediatric:).ti,ab.
18 and 19
from 20 keep (SELECTED REFERENCES)
18 not 21

Combined Premedline/Medline/Embase/Current Contents Cinahl - broad New Zealand search

1 exp asthma/ (52742)
2 asthma.mp. (82944)
3 1 or 2 (83257)
4 new zealand/ or new zealand.mp. (30727)
5 new zealand.in. (57602)
6 4 or 5 (77006)
7 3 and 6 (1343)
8 limit 7 to yr=1997-2000 (691)
9 remove duplicates from 8 (355)
10 (letter or news).pt. (652061)

11 9 not 10 (330)
12 case report/ or case report.mp. (647075)
13 11 not 12 (325)
14 (child: or infan: or pediatric: or paediatric:).ti. (365724)
15 13 not 14 (265)

Cochrane Library Controlled Trials Register

ASTHMA:ME
ASTHMA:TI
#1 OR #2
CHILD OR PEDIATRIC* OR PAEDIATRIC*:TI
#3 NOT #4
LIMIT TO YR 1997-2000

Review databases: Cochrane Library Systematic Reviews & Protocols, DARE, HTA, NHS EED, Best Evidence

Because these databases are small and of such high quality they were searched simply using the word *asthma* then sifted manually for relevant references

Other databases and sources

Other databases and sources without indexing were searched using combinations of the headings and textwords from the above strategies in simple, iterative searches such as:

Asthma AND guideline*
Asthma NOT (pediatric OR paediatric OR child* OR infan* OR copd OR chronic obstructive OR rhinitis)

Appendix 2

EVIDENCE GRADING FORMATS

Intervention

Drug, dose, mode of delivery, duration of treatment.

Abbreviations:

BDP	Budesonide
BEC	Beclomethasone
BMB	Bambuterol
CIR	Circulaire™
CNV	Conventional nebuliser
CON	Continuous dose
CYC	Cyclohaler
D/A	Diskus/Accuhaler
DH	Diskhaler
DPI	Dry powder inhaler
DU	Diskus
FNS	Flunisolide
FP	Fluticasone
FRM	Formoterol
Int	Intermittent dose
IPR	Ipratropium
MNT	Montelukast
PRD	Prednisone
ROT	Rotahaler
SLB	Salbutamol
SLM	Salmeterol
TAA	Triamcinolone
TBH	Turbuhaler
TEB	Terbutaline
THP	Theophylline
ZAF	Zafirlukast

OCS	Oral corticosteroids
ICS	Inhaled corticosteroids
IGS	Inhaled glucosteroids

Mode of delivery

Abbreviations:

CFC	chlorofluorocarbon propellant
D-inh	diskhaler
HFA	hydrofluoroalkane propellant
Iv	intravenous
Im	intramuscular
Inh	inhaler
MDI	metered dose inhaler
Po	oral
Neb	nebuliser

Dose frequency

Abbreviations:

qd	once daily
mane	once in morning
nocte	once at night
bd	twice daily
Qid	four times daily
q4h	every four hours
PRN	as required

Criteria for inclusion and exclusion

Inclusion

- Age range
- FEV_1 as a % of predictive value if available or change in FEV_1 as a percent change due to exercise challenge or ICS or other medication challenge where FEV_1 %pv not available.
- Smoking history

Exclusion

- Prior recent emergency care
- Other relevant and important morbidity

Abbreviations

%PV = % of predicted value
ED = Emergency department
FEV_1 = Forced expiratory volume in one second
ICU = Intensive care unit
PC_{20} = challenge (usually methacholine or histamine) concentration that caused a 20% fall in FEV_1
PEFR = Peak expiratory flow rate
RCT = randomised controlled trial
URTI = upper respiratory tract infection

Results/outcomes

Generally these will relate to POEMs

Drug category in left column relates to drug of efficacy in the trial

Abbreviations:

NNT = numbers needed to treat using the drug of efficacy to achieve one favourable outcome

NNH = numbers needed to harm using the drug of least efficacy to achieve one unfavourable outcome

P value = probability measure of uncertainty

Comments

Specifics regarding population demographics e.g. mean age, sex distribution, and ethnicity, mean FEV1 % PV

Specific asthma subgroup e.g. exercise induced.

Important methodological issues, which might undermine study validity

Concurrent therapy

Appendix 3

S I G N	***Methodology Checklist 1: Systematic Reviews and Meta-analyses***
Study identification *Include author, title, reference, year of publication*	
Checklist completed by:	
SECTION 1: INTERNAL VALIDITY	

Evaluation criterion		*How well is this criterion addressed?*
1.1	Does the review address an appropriate and clearly focused question?	
1.2	*Does the review include a description of the methodology used?*	
1.3	*Was the literature search sufficiently rigorous to identify all relevant studies?*	
1.4	Was study quality assessed and taken into account?	
1.5	Does the review include all the potential benefits and harms of the intervention?	
1.6	Was it reasonable to combine the studies?	
1.7	Do the conclusions flow from the evidence reviewed?	

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code ++, +, or -*	
2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
SECTION 3: DESCRIPTION OF THE STUDY		
3.1	What types of study are included in the review? *Randomized Controlled Trials (RCT), Controlled Clinical Trials (CCT), Cohorts, Case Control Studies*	
3.2	What interventions are considered?	
3.3	What outcome measures are used? *i.e. benefits and harms*	
3.5	Are potential confounding factors considered? *This is particularly important where study types other than RCTs are included in the review.*	
3.6	What are the characteristics of the study population? *e.g. age, sex, disease characteristics of the population, disease prevalence.*	
3.7	What are the characteristics of the study setting? *e.g. rural, urban, hospital inpatient or outpatient, general practice, community.*	
SECTION 4: GENERAL NOTES AND COMMENTS		

S I G N	***Methodology Checklist 2: Randomised Controlled Trials***

Study identification
Include author, title, reference, year of publication

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

Evaluation criterion		*How well is this criterion addressed?*
1.1	Does the study address an appropriate and clearly focused question?	
1.2	*Was the assignment of subjects to treatment groups randomised?*	
1.3	*Were the treatment and control groups similar at the start of the trial?*	
1.4	Was an adequate concealment method used?	
1.5	Were subjects and investigators kept 'blind' about treatment allocation?	
1.6	Are all relevant outcomes measured in a standard, valid and reliable way?	
1.7	Apart from the treatment under investigation, were the groups treated equally?	
1.8	What percentage of the individuals or clusters recruited into the study are included in the analysis? Statistical poweradequacy	
1.9	Were all the subjects analysed in the groups to which they were randomly allocated?	
1.10	Degree of pharmaceutical company involvement	

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code ++, +, or -*	
2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?	
If the study reports an evaluation or comparison of diagnostic tests, please complete a diagnostic studies checklist before completing the next section.		
SECTION 3: DESCRIPTION OF THE STUDY		
3.1	How many patients participated in the study? *Overall number, and in each arm of the study.*	
3.2	What was the scale and direction of the measured effect?	
3.3	What are the characteristics of the study population? *e.g. age, sex, disease characteristics of the population, disease prevalence.*	
3.4	Are there any specific issues raised by this study? *Make any general comments on the study results and their implications*	